National Center for
Research Resources

U. S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health

Program Highlights

National Center for Research Resources

The National Center for Research Resources (NCRR) supports NIH intramural and extramural biomedical research that includes clinical studies, development and studies of animal and other disease models, basic biomedical research, and instrumentation research. NCRR also supports the operation of instrumentation and computer facilities as well as research centers in academic institutions with large minority enrollments. In addition, NCRR provides the NIH intramural scientific community with library services and medical arts and photography services. The activities and services of the NCRR—and publications that describe them—are listed below. For more detailed information about particular NCRR programs or the resources they support, contact the program directors at the numbers listed below.

NCRR Extramural Research Resources

comprise seven programs:

- **Biological Models and Materials Research.** *Telephone: (301) 402-0630;*
- **Biomedical Research Support.** *Telephone: (301) 496-6743;*
- **Biomedical Research Technology.** *Telephone: (301) 496-5411;*
- **Comparative Medicine.** *Telephone: (301) 496-5175;*
- **General Clinical Research Centers.** *Telephone: (301) 496-6595*
- **Research Centers in Minority Institutions.** *Telephone: (301) 496-6341;* and
- **Research Facilities Improvement.** *Telephone: (301) 496-5411*

NCRR Intramural Research Resources

comprise two programs and two branches:

- **Biomedical Engineering and Instrumentation Program.** *Telephone: (301) 496-4741;*
- **Library Branch.** *Telephone: (301) 496-2447;*
- **Medical Arts and Photography Branch.** *Telephone: (301) 496-2868*
- **Veterinary Resources Program.** *Telephone: (301) 496-2527.*

NCRR Publications:

- The *Research Resources Reporter* is a monthly newsletter that describes NCRR-supported biomedical findings and research in progress at universities, medical centers, and other research institutions across the United States. The *Reporter* also describes research services available to biomedical investigators and publishes a question-and-answer column relating to research resources.
- The *NCRR Program Highlights* is an annual report of the research accomplishments and significant services of each NCRR program and branch during the fiscal year. Detailed budget information about NCRR is also provided.
- The NCRR *General Clinical Research Centers Directory* contains information about General Clinical Research Centers, their staffs, resources, and major areas of investigation. Investigators who receive their primary research funding from the National Institutes of Health or the Alcohol, Drug Abuse and Mental Health Administration are eligible to perform clinical research studies at one of the more than 70 centers.
- The NCRR *Biomedical Research Technology Resources Directory* lists resource centers supported by the Biomedical Research Technology Program, their staffs, resources, and major areas of investigation. The facilities are dedicated to applying the latest advances in the physical sciences, mathematics, computer science, and engineering to biomedical research. The facilities and their services are available to qualified investigators.
- The NCRR *Resources for Comparative Biomedical Research Directory* contains information about specialized animal research and supply facilities, their staffs, types of resources, and major areas of research. The resources range from breeding facilities for lower animal forms to nonhuman primate research centers. These facilities and their services are available to qualified investigators.

All NCRR directories are updated and reissued approximately every 15 months.

Single copies of NCRR publications may be obtained free of charge from the Research Resources Information Center, 1601 Research Boulevard, Rockville, MD 20850. Telephone: (301) 251-4970.

Queries about the NCRR may be directed to the Office of Science and Health Reports, National Center for Research Resources, 5333 Westbard Avenue, Westwood Building, Room 10A15, Bethesda, MD 20892. Telephone: (301) 496-5545.

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Program Highlights

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ANNUAL REPORT

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A Brief Preface to the 1990 Annual Report of the National Center for Research Resources

The National Center for Research Resources (NCRR) of the National Institutes of Health (NIH) was established on February 15, 1990, through a merger of the NIH Division of Research Resources (DRR) and Division of Research Services (DRS). The programs that were derived from DRR constitute the NCRR Extramural Research Resources (ERR); the programs and branches derived from DRS constitute the NCRR Intramural Research Resources (IRR). The Center develops a wide variety of research resources and ensures their availability, thereby strengthening and enhancing biomedical research supported and performed by NIH. Through its ERR programs, NCRR provides resources to NIH-supported institutions; through its IRR programs and branches, it provides services and resources to the intramural research programs of NIH.

In fiscal year 1990 the appropriations for the ERR programs administered by NCRR amounted to $371.7 million from which the Center made awards totaling $357.8 million. The remainder of the funds provided technical and personnel support required for administration of the programs. The IRR programs and branches are supported by the NIH Management Fund (a small percentage of the funds appropriated for the NIH intramural research programs) and by the NIH Service and Supply Fund (a fee-for-service mechanism). In fiscal year 1990 the NCRR Management Fund totaled $17.9 million and the Service and Supply Fund income was $31.1 million. A more detailed breakdown of the 1990 funding is summarized in the tables preceding the ERR and IRR sections respectively of this annual report.

Each of the extramural programs has a major impact on biomedical research in the United States. They comprise the General Clinical Research Centers Program, Biomedical Research Technology Program, Comparative Medicine Program (formerly the Animal Resources Program), Biomedical Research Support Program, Biological Models and Materials Research Program, and Research Centers in Minority Institutions Program. Similarly, the intramural programs and branches contribute markedly to the planning, performance, and reporting of NIH intramural research. They comprise the Biomedical Engineering and Instrumentation Program, Library Branch, Medical Arts and Photography Branch, and Veterinary Resources Program.

The mission, scope of support, and significant accomplishments of each program or branch during the year are described in the following sections of Program Highlights 1990.

Robert A. Whitney, Jr., D.V.M.
Director, National Center for Research Resources
National Institutes of Health

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Overview of Extramural Research Resources Activities

National Center for Research Resources Overview of Extramural Research Resources FY 1990 Activities

Program	Funding	Major Resources Supported
General Clinical Research Centers Program	$115,746,000	• 77 General Clinical Research Centers • 43 Clinical Associate Physicians • 1 small business innovative research grant • Computerized Data Base Management and Analysis Systems (CDMAS) • Cofunded MBRS grant to Meharry Medical College GCRC • cofunded 2 conference grants
Biomedical Research Technology Program	$ 43,590,000	• 54 Biomedical Research Technology Resource Centers • 5 research project grants • 4 resource-related project grants • 14 small business innovative research grants • 14 small grants • PROPHET computer network
Comparative Medicine Program	$ 67,696,000	• 7 Regional Primate Research Centers • 41 Laboratory Animal Research Resource Centers • 17 research project grants • 20 resource-related research project grants • 51 animal facility improvement awards • 11 research career awards in laboratory animal sciences • 17 postdoctoral research training programs • 4 small business innovative research grants • Chimpanzee Breeding and Research Program • Specific-Pathogen-Free Rhesus Monkey Breeding and Research Program
Minority Biomedical Research Support Program	$ 29,104,000	• Funds transferred to NIGMS to support MBRS awards
Biomedical Research Support Program	$ 78,838,000	• Biomedical Research Support Grants awarded to 629 institutions • 144 Shared Instrumentation Grants • 358 Minority High School Student Research Apprentice Program awards to support 1,406 students
Biological Models and Materials Research Program	$ 5,344,000	• 4 Biological Models Research Centers • 9 research project grants • 4 resource-related research projects
Research Centers in Minority Institutions Program	$ 15,312,000*	• 17 RCMI awards
Total Extramural	$357,821,000**	

*Funded through an appropriation to the Office of the Director, National Institutes of Health. In addition, the National Institute of Allergy and Infectious Diseases provided $1,267,719 in cofunding for AIDS research and the National Institute of Mental Health provided $144,000 in cofunding for mental health research infrastructure.

**In addition, $412,000 of reimbursable authority from other Federal agencies was obligated by NCRR for FY 1990.

General Clinical Research Centers Program

Program Description

The General Clinical Research Centers (GCRC) Program, initiated in 1960, is celebrating its 30th anniversary this year. The primary mission of the GCRC Program is to provide the clinical research infrastructure to investigators who receive their primary research funding from the other components of the National Institutes of Health (NIH) and the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA). As a result, the research hosted at GCRC sites reflects the research missions of the several NIH categorical institutes and centers. Investigators carrying out research in the GCRC's received almost $1 billion of primary research support in FY 1990. The national network of 77 centers hosted 6,724 investigators who received $799.6 million in primary research support from the other components of the NIH and ADAMHA for a wide range of studies in both children and adults. The remaining primary research support, approximately $150 million to $200 million, was derived from other federal agencies, state governments, private foundations, and industry.

The national network of centers accounted for 31,498 admissions with an average length of stay of 3.8 days. This length of stay is approximately half that of the national average for patients admitted to hospitals across the country for established medical care. The cost of hosting clinical research at the centers continues to rise at rates far exceeding the U. S. Department of Commerce Biomedical Research and Development Price Index because of rapidly increasing hospital-based costs for inpatient studies as well as the continuing rise in salaries for nursing staff. Those two components, both increasing at annual rates of 15 to 20 percent, account for 70 percent of the entire GCRC budget. The national network of GCRC's is analogous to a 600-bed research-intensive hospital with approximately 120,000 research patient days and more than 200,000 outpatient visits for research studies. Outpatient visits range from 30 minutes up to 12 to 14 hours. However, the "research hospital" is distributed among 77 geographically separate sites across the country. The GCRC's provide the clinical research infrastructure to facilitate clinical research—the specialized research nurses, research dietitians, biostatisticians, computer systems managers, computer hardware and software for data base management and analyses, as well as the research facilities for both inpatient and outpatient studies together with their hospital-based research ancillary costs.

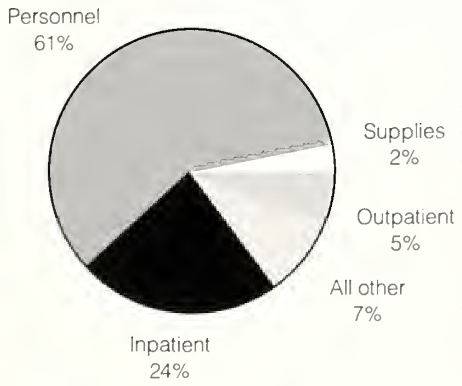
The array of research carried out in GCRC's is almost equally divided among biotechnology, clinical trials, prevention, and other studies. Investigators at the centers now focus on research that requires more sophisticated technologies such as molecular genetic techniques, magnetic resonance spectroscopy for in situ metabolic studies, positron emission tomography, and other advanced imaging techniques.

The nature of clinical research has changed dramatically since the first eight GCRC's were funded in 1960. In the early years of the GCRC Program investigators made key contributions to transplantation research. These early efforts and continued progress have resulted in established medical techniques for enhancing the success of kidney, bone marrow, liver, and other organ transplants. The "Bubble Boy," a long-term patient at one of the GCRC's, advanced our knowledge of severe combined immunodeficiency diseases (SCID's) and their specific etiologies. The first patient to receive gene therapy for adenosine deaminase deficiency, one cause of SCID, is a patient at one of the GCRC's. Undoubtedly, GCRC-based investigators will be the "trail blazers" for gene therapy for several diseases for which no effective therapy currently exists.

Research on acquired immunodeficiency syndrome (AIDS) continues to be a major focus, with progressively more research centering on pediatric consequences of HIV infection. Currently, 57 of the 77 centers host one or more research studies on AIDS. The number of AIDS-related research projects hosted at the centers was 286, a 55-percent increase compared to the number of projects in the previous year. The network of GCRC's plays an integral role in hosting research protocols for the AIDS Clinical Trials Groups as well as other investigator-initiated HIV-related research.

The GCRC Program continues to acknowledge the clinical investigator's important role in utilizing basic research results in clinical studies. Dr. Rebecca Buckley, the J. Biren Sid-

General Clinical Research Centers Budget Distribution FY 1990



As of 8/13/90

bury Professor of Pediatrics and chief of the division of pediatric allergy and immunology at Duke University Medical Center, received the Second Annual General Clinical Research Centers Award for Excellence in Clinical Research; the award was presented at the plenary session of the national meeting of the American Society for Clinical Investigation in Washington, D.C.

Research Highlights

Aging

Osteoporosis in Men. The development of age-related bone loss in men was explored by investigators working in the GCRC of the University of Oregon in Portland. Their studies were conducted among a group of 77 healthy men 30 to 85 years old.

Over a 3-year period the Oregon scientists found that these men had a greater rate of bone mineral loss than was previously recognized. Their findings may help to explain recent reports of an increasing incidence of bone fractures in men in the United States.

Efforts to prevent the bone loss by dietary calcium supplements were unsuccessful. Moreover, the investigators' evaluation of the proposed effectiveness of calcium supplements in lowering blood pressure revealed that an increased intake of dietary calcium by these healthy men had no effect on their blood pressure.

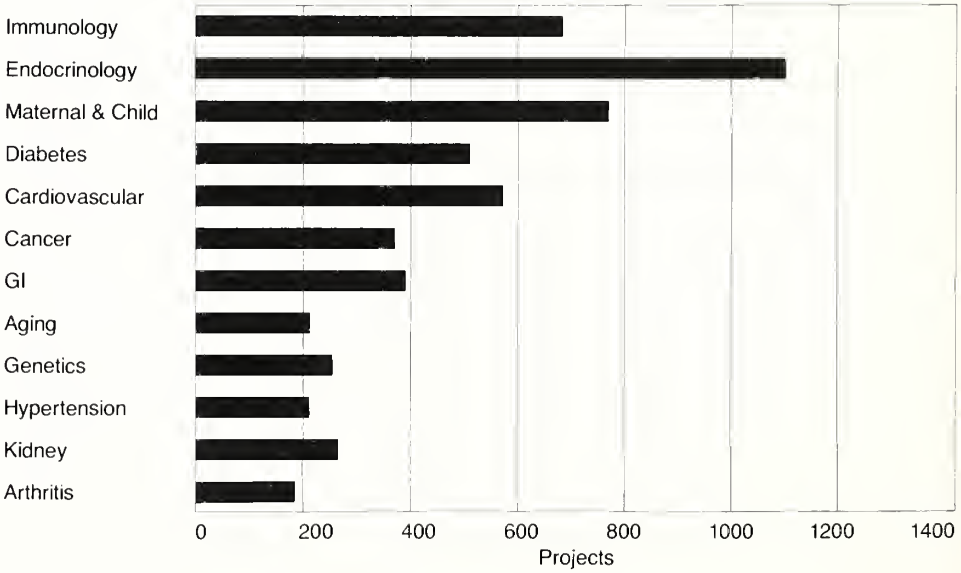
Alzheimer's Disease. At the University of Washington GCRC in Seattle 205 healthy, elderly volunteers considered at risk for Alzheimer's dementia (AD) by virtue of family history or mild memory problems were subjects in a long-term study. Participants were evaluated using an all-night sleep electroencephalogram (EEG) and assessment of biological and hormonal factors.

In preliminary studies the investigators report that their EEG technique can distinguish patients with Alzheimer's disease from non-Alzheimer individuals (normal controls or patients with major depressive disorder) at a 90-percent accuracy rate. The approach is based on computer-assessed quantification of high-frequency (beta) and low-frequency (theta) activity in the EEG during key periods of sleep known as rapid-eye-movement (REM) sleep. The Seattle scientists think the EEG measurements during REM sleep have potential value in diagnosing those at risk of Alzheimer's dementia. They note that identification of an AD risk population would improve clinical studies of proposed intervention therapy in early AD. In addition, such a diagnostic tool might comfort many seniors who have grave concerns about their memory but do not have AD. The study is expected to continue over a 10-year period.

AIDS

Many GCRC's throughout the United States, under the auspices of the NIH-supported AIDS Clinical Trials Group (ACTG), are devoting significant efforts and resources to research on the therapy of AIDS and the opportunistic infections associated with AIDS.

General Clinical Research Centers Program



Among the agents being studied at the GCRC's are zidovudine (azidothymidine or AZT), interferon, interleukin-2, acyclovir, pentamidine, spiramycin, ganciclovir, gammaglobulin, granulocyte-macrophage colony-stimulating factor, recombinant soluble CD4 (receptin), 2′,3′-dideoxyinosine (ddI), dideoxycytidine (ddC), and 3′-azido-2′,3′-dideoxyuridine (AzdU). Many of the studies have advanced from phase 1 clinical evaluation to phase 2 and phase 3, and have progressed beyond the carefully controlled environments of the GCRC's to more widespread clinical testing at many medical centers.

Phase 1 studies of dideoxyinosine (ddI), an inhibitor of the enzyme reverse transcriptase of the human immunodeficiency virus (HIV), have been conducted at the GCRC at the University of Rochester in New York. In these studies ddI was administered to 28 patients with AIDS or AIDS-related complex (ARC), a condition that progresses over time to full-blown AIDS. To determine the pharmacokinetics and the maximum tolerated dose of ddI, the drug was given in a sequentially escalating dose intravenously for 2 weeks and then orally for 8 to 15 weeks. Bioavailability of ddI after oral doses was 40 to 50 percent; some toxicity was observed.

An important indicator of anti-AIDS effectiveness, a significant sustained increase in the level of the white blood cells called CD4 lymphocytes, was seen in 8 of 13 ddI-treated patients. Another indicator of lessening disease, a decline in the serum concentration of HIV p24 antigen, was also observed with ddI. After treatment, 8 of the 10 patients who had detectable p24 antigen at entry into the study temporarily had a greater than 50 percent decrease in blood levels of the antigen.

Continuing studies of ddI and other potential anti-AIDS drugs are under way at the University of Rochester and many other GCRC's across the United States.

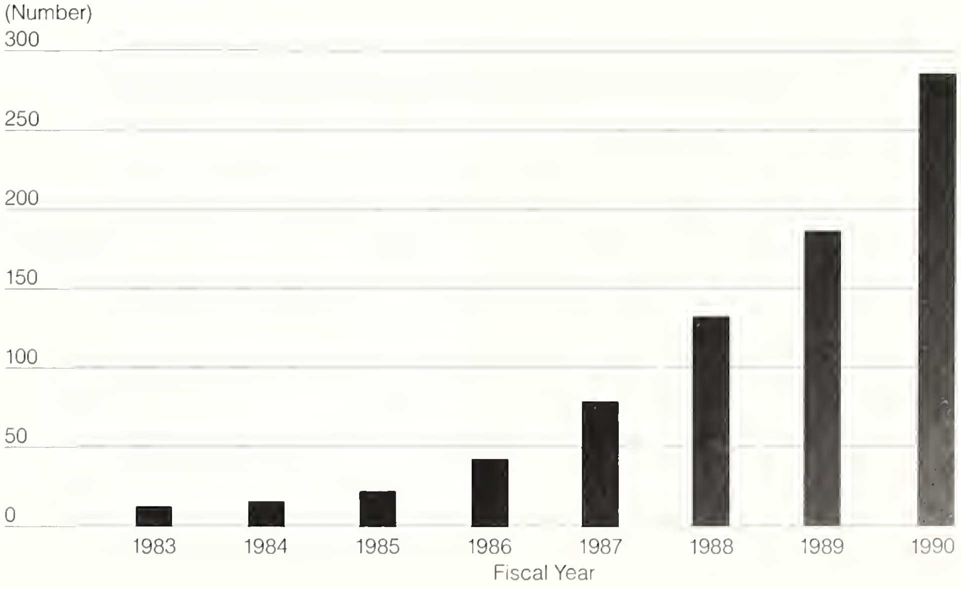
Cancer

Evaluations of the therapeutic effects of the immune modifier interleukin-2 (IL-2) in patients with cancer were conducted at the New England Medical Center Hospital GCRC in Boston, Massachusetts, during the year. The results suggested that IL-2 effectiveness against a patient's cancer may be linked to damage to the thyroid gland.

IL-2 was administered in high-dose intravenous infusions alone or in combination with lymphokine-activated killer (LAK) cells, which help destroy tumor cells. Of 115 patients who received IL-2 therapy, 17 developed thyroid insufficiency; the majority had a pretreatment finding of antithyroid antibodies.

One of the most striking findings of the study was a correlation between the presence of an autoimmune thyroid reaction and tumor regression. Thirteen of the 17 patients with thyroid dysfunction (77 percent) showed tumor regression that ranged from minor to complete. In contrast, only 27 percent of the patients who had normal thyroid function had a favorable response to IL-2. The investigators suggest that an autoimmune predisposition may indicate a favorable outcome of IL-2 therapy and that autoimmune destruction of a tumor may make a major contribution to the efficacy of IL-2.

General Clinical Research Centers
AIDS-Related Research Projects



Diabetes

Defect in Glucose Metabolism. A major diabetic defect in persons with non-insulin-dependent diabetes mellitus (NIDDM) has been localized to muscle tissue by scientists working in GCRC's at Yale University in New Haven, Connecticut, and at the University of Texas Health Science Center in San Antonio.

Using nuclear magnetic resonance (NMR) spectroscopy, the scientists showed that persons with NIDDM convert glucose to glycogen, its starchlike storage form, at only half the rate of normal individuals. In addition, they showed that in both normal and diabetic persons almost all glucose conversion to glycogen takes place in the muscles. The NMR spectroscopic data confirm earlier conclusions that were based on indirect evidence.

The highly sophisticated clinical maneuvers leading to these findings were performed in New Haven with the participation of five men with NIDDM and six healthy, age-matched controls without a family history of diabetes.

The report by the New Haven and San Antonio scientists may necessitate some medical textbook revisions; many texts now erroneously state that after a meal glucose is stored as glycogen primarily in the liver.

Endocrinology and Metabolism

Parathyroid Hormone and Paget's Disease of Bone. Studies reported by scientists at Columbia-Presbyterian Medical Center in New York City indicate that high blood levels of parathyroid hormone, a regulator of metabolic activity in bone, appear to correlate with the severity of Paget's disease of bone. In this disorder localized areas of normal bone are broken down and replaced by abnormal bone tissue.

Thirty-nine patients 53 to 91 years old in varying stages of Paget's disease were studied at this New York City GCRC. Abnormally high levels of parathyroid hormone were found in seven of the most severely affected patients.

Now the investigators are evaluating the effects of large doses of oral calcium in these patients because high blood levels of calcium normally inhibit the release of parathyroid hormone by the parathyroid gland. A double-blind, placebo-controlled evaluation of whether calcium "repletion" might influence the pagetic process is in its preliminary stages.

A pancreas transplantation is performed by a surgical team at the University of Minnesota GCRC in Minneapolis in a patient with insulin-dependent diabetes mellitus.

University of Minnesota

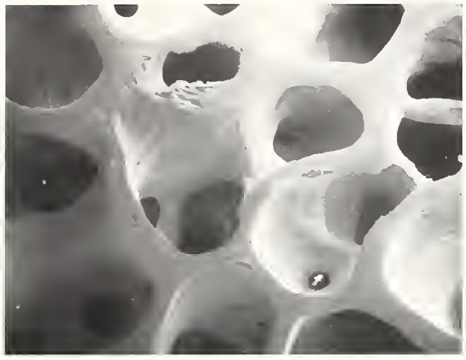
Ulcer Medication Causes Estrogen Imbalance in Men. The origin of feminizing changes induced in some men by the antiulcer medication cimetidine was deciphered in 1990 by scientists at the Rockefeller University Hospital GCRC in New York City. The scientists found that cimetidine decreased the normal metabolic degradation of the female sex hormone estradiol.

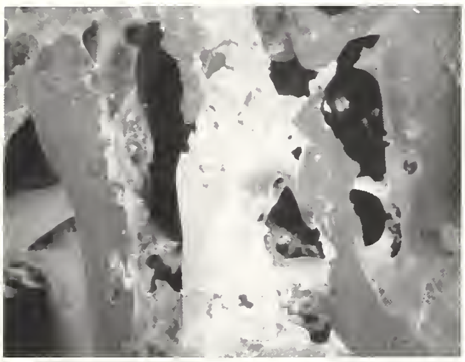
Cimetidine's adverse effects such as male breast enlargement and sexual impotence were recognized in recent years.

The New York City investigators studied the effects of cimetidine in nine healthy men 23 to 48 years old who were admitted to the GCRC at Rockefeller University. Earlier studies with rats had disclosed that cimetidine, by binding to cytochrome P450 enzymes in the liver, decreased that organ's ability to metabolize or degrade estradiol.

After cimetidine administration, the investigators found that the principal metabolic process that converts estradiol to less powerful estrogens had declined 40 percent in the men; their blood concentration of estradiol rose by 20 percent. In contrast, the antiulcer medication ranitidine, which has not shown feminizing effects, did not block the normal biotransformation of estradiol.

The investigators are now studying the effects of cimetidine in women, the population group most affected by estrogen-dependent diseases. Osteoporosis and cancers of the breast, endometrium, and cervix have been associated with differing estrogen levels, but the exact relationships are unclear.





Normal bone (top) and abnormal bone of a Paget's disease patient are shown in scanning electron micrographs. Research on Paget's disease at Columbia-Presbyterian Medical Center GCRC in New York City links a rise in parathyroid hormone level with the severity of this bone disorder.

Dr. David Dempster, Mary Ann Liebert, Publisher, and J. B. Lippincott Co.

Genetic Diseases

Cystic Fibrosis. A family of northern European descent that carries a cystic fibrosis (CF) gene and has lived in North Carolina since the late 1700's is being studied by GCRC-aided investigators at the University of North Carolina (UNC) at Chapel Hill and at Duke University in Durham. The DNA of family members was analyzed to clarify their inheritance of a mild genetic variant of CF. The disease in these patients, unlike common CF, does not lead to pancreatic insufficiency or life-threatening pulmonary problems.

Recently, the UNC investigators also reported that a diuretic drug, amiloride, appeared to slow the pace of damaging lung disease when it was administered as an aerosol to patients with classic CF. Aerosolized amiloride did not reverse existing airway damage. However, it seemed to block removal of water from the bronchial mucus, keeping the mucus thin enough to be coughed up relatively easily. Although treatment results must be confirmed in a larger number of patients, aerosolized amiloride is the first therapeutic approach directly targeted to the cell membrane abnormality now believed linked to the basic gene defect in CF.

Progress in Treating Gene Disorder of Carnitine Deficiency. Investigators at the GCRC at the Children's Hospital of Philadelphia, Pennsylvania, recently reported progress in studies of a rare disease of fatty acid oxidation caused by deficiency of carnitine, a small molecule that is required for transport of fatty acids into the mitochondria of cells. In the mitochondria fatty acids are broken down to produce energy for muscles. Children born with the defect have weakened heart and skeletal muscles and life-threatening episodes of hypoglycemia and coma. After the Philadelphia scientists identified an initial case of primary carnitine deficiency, 14 other children were found who had the deficiency.

The investigators have used orally administered carnitine to treat the patients in the study. The carnitine replacement therapy effectively corrected the impairment in fatty acid oxidation, normalized cardiac function, and eliminated the problem of hypoglycemia and coma. However, muscle levels of carnitine remain low in these children.

Male Pseudohermaphrodites with Enzyme Deficiency. Research at the Cornell University Medical Center GCRC in New York City has made substantial contributions toward delineating the major actions of the hormones testosterone (T) and dihydrotestosterone (DHT) on male sexual differentiation and development. One focus of the research has been a study of 38 male pseudohermaphrodites from 23 families in the Dominican Republic. These pseudohermaphrodites, individuals who have gonadal tissue of one sex but inconclusive external sex characteristics, had an inherited deficiency of the enzyme 5-alpha-reductase, which is required for production of dihydrotestosterone. The mode of inheritance was autosomal recessive.

The men were admitted to the GCRC at Cornell as part of continuing research into the particular biological effects of T and DHT; deficiency of DHT has been associated with incomplete development of male external genitalia. In the continuing studies they are being evaluated to determine DHT's role in the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH).

Heart Disease

Truncal Obesity Predicts Levels of HDL-2 Cholesterol. Investigators at the Washington University GCRC in St. Louis, Missouri, suggest that upper body obesity in healthy, nonsmoking older men and women is linked to an increased risk of heart disease through low levels of a cholesterol compound. The investigators found low levels of high-density lipoprotein-2 (HDL-2) cholesterol, the "good" cholesterol, in a group of 146 men and women with upper body obesity.

In addition to HDL-2, several related covariate factors reflecting body weight, fatness, regional distribution of fat, glucose tolerance, plasma insulin level, diet, and fitness were analyzed in a mathematical model.

The investigators concluded that HDL-2 levels are inversely correlated with truncal fat, plasma insulin levels, and the presence of glucose intolerance. Interestingly, HDL-2 cholesterol levels were not related to body mass index, total percentage of body fat, maximal oxygen uptake, diet, or the sex of persons in this study group.

Metabolic Differences Between Fat Cells. Body fat distribution has been identified as an important variable in determining the metabolic abnormalities associated with obesity. To determine whether upper body fat cells metabolize fat differently from lower body fat cells, investigators at the Mayo Foundation GCRC in Rochester, Minnesota, studied 10 women with upper body obesity, 9 women with lower body obesity, and 8 nonobese women. The women remained in the GCRC overnight, and their fat metabolism was evaluated under basal conditions (after a meal) and under conditions in which the fat metabolism was stimulated or suppressed.

The investigators found that after a meal upper-body-obese women built up fat faster than did lower-body-obese women. In addition, administration of the hormone epinephrine, which stimulates breakdown of fat, produced a smaller effect in upper-body-obese women than in women with lower-body obesity.

The Mayo Clinic scientists conclude that differences exist among fat cells—either between individuals or within an individual—and these differences may affect the metabolic aberrations associated with different types of obesity.

Hypertension

Potassium Reported Important in Blood Pressure Regulation. Earlier epidemiologic studies have suggested an inverse relationship between potassium in the diet and the prevalence of hypertension, high blood pressure. Investigators at the GCRC at Temple University in Philadelphia, Pennsylvania, explored the potassium effect in a study of eight persons with high blood pressure.

The Philadelphia scientists administered diets containing low or high concentrations of potassium to the hypertensive patients and monitored their blood pressure and the blood and urine levels of sodium and potassium. The mean arterial blood pressure was highest in patients on the low-potassium diet. The average daily excretion of sodium and potassium and the blood level of potassium were both lower in patients on the low-potassium diet than in those on the high-potassium diet. When challenged with a saline infusion, persons in both groups responded with higher mean arterial blood pressures, but the rise was greater in those on the low-potassium diet.

The Philadelphia investigators conclude that potassium depletion induces sodium retention and elevation of the blood pressure of persons with high blood pressure. They plan further studies to clarify the mechanism of potassium-induced changes.

Magnesium Supplements Evaluated for Antihypertensive Effect. Scientists at the University of Southern California GCRC in Los Angeles have been studying high blood pressure and atherosclerosis among diabetics in an effort to learn the mechanisms that produce a higher-than-normal risk of heart disease in this population. In a recent study the California investigators attempted to clarify whether the intracellular levels of free magnesium in diabetic patients are lower than normal, and whether magnesium supplements might reduce blood pressure and the potentially hazardous clumping of blood platelets that may lead to blood clots in these patients.

The investigators studied patients with diabetes and found a deficiency in intracellular magnesium. After magnesium supplements were administered orally for 8 weeks, the scientists found that blood pressure and platelet aggregation were both markedly reduced in these patients. Production of thromboxane, a substance released by platelets that induces platelet clumping and constricts blood vessels, was inhibited as well.

The Los Angeles investigators suggest that magnesium supplements may provide a new approach to the treatment of diabetic patients that may lower their risks of high blood pressure and hardening of the arteries.

This psoriasis patient's hands have red patches, or plaques, covered by the thick silvery scales that are characteristic of the disease. Abnormal growth of cells in psoriasis, a chronic skin disorder affecting about 4 million Americans, has been linked to high levels of the cell growth factor interleukin-6 in keratinocytes, the outermost skin cells. The research on psoriasis was conducted in the GCRC of Rockefeller University Hospital, New York City.

Courtesy of the Rockefeller University

Immune Responses and Immune Modifiers

Interleukin-6 Linked to Psoriasis. New findings by investigators at the Rockefeller University GCRC in New York City have provided basic information that may lead to therapeutic benefits for the 4 million Americans with the chronic skin disorder psoriasis. The scientists found that psoriatic skin plaques from patients with psoriasis contain high levels of the cell growth factor interleukin-6 (IL-6) and its corresponding messenger RNA. Their studies of 35 psoriasis patients showed that IL-6—a cytokine secreted by fibroblasts, endothelial cells, and macrophages—stimulates rapid growth of the outer-layer skin cells called keratinocytes, a growth phenomenon that characterizes psoriasis. This is the first evidence that IL-6 levels are increased in active psoriatic plaques and the first indication that IL-6 stimulates keratinocytes to divide.

Skin of patients treated by anti-inflammatory medications contained less IL-6 after treatment than before; the changes correlated with resolution of the psoriatic plaques. A team of Rockefeller scientists is now studying the results of treating skin plaques with the immunosuppressant cyclosporine.

Interferon-Alfa Temporarily Blocks Liver Damage of Hepatitis C. A cooperative study by the Hepatitis Interventional Therapy Group, which includes four GCRC's, was undertaken to assess the therapeutic potential of the immunomodifier interferon-alfa in 166 patients with chronic hepatitis C. Formerly known as non-A, non-B hepatitis, hepatitis C is a debilitating viral disease of the liver that sometimes progresses to fatal cirrhosis.

In the study 166 patients were randomly assigned to receive recombinant interferon-alfa in doses of 1 million or 3 million units for 24 weeks or to receive no treatment. Response to therapy was measured by declining blood levels of the enzyme alanine aminotransferase, an indicator of liver damage.

The investigators found that the marker enzyme decreased to normal or near normal levels in 46 percent of patients receiving the higher dose of interferon, in 28 percent of those receiving the lower dose, and in only 8 percent of the untreated patients. In addition, liver biopsy specimens showed improvement in about one-half of the patients treated with high-dose interferon and in more than one-fourth of those given the lower dose.

As part of a new study, the GCRC-supported scientists are now attempting to modify the interferon dosage to improve the encouraging response rate.

Lead Poisoning

Lead Poisoning in Children May Be Treatable With New Agent. Children affected by lead poisoning are at risk of long-term damage to the nervous system. Urban children exposed to auto exhaust from leaded gasoline and lead paint in dilapidated buildings are at particular risk.

For several years, scientists at the pediatric GCRC at Johns Hopkins University in Baltimore, Maryland, have been studying agents for treating this critical problem that is often mistaken for mental retardation. During the past year these scientists have explored the usefulness of two new agents that are water-soluble analogs of 2,3-dimercapto-1-propanol (BAL), a compound that they investigated earlier. They report that both of the new drugs are less toxic than BAL and the calcium disodium salt of EDTA ($CaNa_2EDTA$), another compound previously used in lead poisoning. In studies with animals the latter agent was found to transport lead to the brain. Both of the new drugs can be given orally.

One of the new agents, 2,3-dimercaptosuccinic acid (DMSA), was found to be particularly promising. A pilot study in 4 children was undertaken to explore dose levels of DMSA; then 10 children were given oral DMSA. The Baltimore scientists report that the children's blood lead levels decreased steadily during the treatment to a safe level of 10-15 micrograms/dL or less.

They report that DMSA has low toxicity, is convenient for oral administration, and has effective chelating action on lead without causing the loss of essential elements such as copper or zinc.

Nutrition

Some Children Benefit From Zinc Supplements. In a randomized placebo-controlled study conducted at the University of Colorado pediatric GCRC, zinc supplementation resulted in accelerated weight gain over a period of several months for some infants and toddlers with markedly delayed growth. Earlier the University of Colorado scientists had shown that zinc supplements increased food intake in some older children.

The 50 children entered in the current zinc study were 8 to 27 months old and weighed considerably less than expected for their ages. They were matched for age, sex, weight, and ethnic origin and given daily treatment with either zinc sulfate in cherry syrup or a placebo.

The difference in weight gain observed between treated and control children was greatest at 3 months and had narrowed by 6 months. The scientists suggest that compliance with the zinc supplementation regimen may have fallen off during the second 3-month period of the study or alternatively, that the zinc deficiency may have been fully corrected during the first 3 months.

Further exploration of the effects of zinc will be conducted at the Denver GCRC utilizing the university's Clinical Mass Spectrometry Resource, which is supported by the Biomedical Research Technology Program of NCRR. With the assistance of this resource the investigators will administer stable isotopes of zinc safely to infants and toddlers to clarify the absorption and disposition of dietary zinc.

The investigators note that young infants usually obtain zinc from breastmilk and that most infant formulas are also enriched with zinc. They caution that zinc deficiency, which is associated with reduced appetite, is only one of many possible factors in an infant's failure to thrive. They do not recommend routine zinc supplementation for all babies who fail to thrive.

In patients with food hypersensitivity, foods such as wheat, eggs, milk, fish, soybeans, and peanuts can cause certain cells to release a cytokine that induces mast cells to release histamine, the chemical that causes allergic symptoms. These immune reactions are being studied in children at the pediatric GCRC of the Johns Hopkins University School of Medicine, Baltimore.

James P. Swyers

Weight Loss and Metabolic Factors After Menopause. Investigators at the University of Alabama in Birmingham conducted a metabolic study of 24 mildly obese and 16 lean, never obese postmenopausal Caucasian women in the university's GCRC. After the mildly obese women achieved a weight reduction of 25 percent, all of the women were placed on a diet identical in composition.

The investigators compared the resting metabolic rate (RMR) as well as dietary thermogenesis—the energy expended in the assimilation and metabolism of foodstuffs—between the two groups of women. They found no significant differences in RMR between obese women who had lost weight and the lean women, but when the obese women lost weight their RMR decreased.

However, significant differences were observed in dietary thermogenesis between the obese and lean conditions but not between the obese and postobese conditions. The data suggest that there is an inherent defect in the thermic response to food in the obese condition that is not corrected after significant weight reduction.

Parkinson's Disease

Deprenyl Given in Early Stage Parkinsonism Slows Disease. In a clinical evaluation known as DATATOP (deprenyl and tocopherol antioxidative therapy of parkinsonism) that includes 34 investigators at 28 medical centers, the drug deprenyl was found to significantly delay the onset of debilitating symptoms and to lengthen the time that persons with Parkinson's disease may enjoy productive employment.

Parkinson's disease is a neurologic disorder resulting from the degeneration of certain cells in the brain that produce the neurotransmitter dopamine. Dopaminergic nerve cells are necessary for movement and balance; deterioration of these cells increasingly disturbs an individual's motor skills.

Fourteen of the centers participating in DATATOP used General Clinical Research Centers. Although the deprenyl study was designed as a 5-year study, preliminary results obtained in one group of patients reached statistical significance early and prompted a revision in planning after an average followup of only 2 years.

Eight hundred patients with a mean age of 61 years who had previously untreated stage I or stage II Parkinson's disease were randomly assigned to one of four subgroups in the study. The patients received various combinations of deprenyl, tocopherol, and placebo preparations. The endpoint of the study for each patient was onset of a disability level that would require administration of the antiparkinsonism drug levodopa.

Of 401 patients in a treatment group that did not receive deprenyl, 176 individuals reached the endpoint within 2 years and required levodopa. In contrast, only 97 of the 399 patients in subgroups that received deprenyl reached that endpoint. The difference was highly significant statistically and prompted the modification of the study. Patients in all groups now receive deprenyl, and the study is continuing.

Tryptophan-induced illness, which is known as eosinophilia-myalgia syndrome, is under study at many centers. Contaminated batches of the dietary supplement tryptophan have been traced to a single foreign manufacturer. Dr. Richard Silver, assisted by head nurse Pat Griffin, examines a patient with tryptophan-induced illness in the General Clinical Research Center at the Medical University of South Carolina in Charleston.

Medical University of South Carolina

Biomedical Research Technology Program

Program Description

The Biomedical Research Technology Program (BRTP) was established to foster development and use of the most advanced technologies by the biomedical research community. BRTP funding enables grantee institutions to establish centers with state-of-the-art technology and advanced equipment that is among the best in the world. At BRTP centers members of the biomedical research community can use the latest high-tech devices in investigative projects, whether or not they are affiliated with the center. The centers also provide training to extramural users and disseminate information about technologies developed at the centers.

The BRTP funds 54 Resource Center Grants and several other types of grants, including Resource Development Grants, Individual Investigator Research Grants, First Independent Research Support and Transition (FIRST) Grants, Small Grants for Innovative Technology, and Small Business Innovative Research Grants. The BRTP is also authorized to award conference grants, Academic Research Enhancement Awards (AREA), cooperative agreements, and contracts to carry out its mission. In FY 1990 the NCRR provided $43.6 million for the BRT Program. Approximately $32.5 million were spent in support of the BRTP resource centers.

The resource centers conduct research in biomedical computer technology and software development and in the engineering of instruments that advance and facilitate studies of molecular and cellular structure and function. Staff scientists at the centers encourage cooperative studies that will ensure extensive use of the sophisticated instruments in all appropriate areas of biomedical research. Among the available instruments are high and intermediate voltage electron microscopes; advanced laser instrumentation; mass spectrometers; magnetic resonance spectrometers; x-ray diffraction instruments; and a variety of computer systems used for molecular interaction studies, simulation, modeling, image analysis, and supercomputing.

In addition to the resource center grants that fund large projects whose feasibility has been accepted, the BRTP also supports small-scale projects to stimulate the development, often by a single investigator, of new and unproved equipment and procedures. Approximately 15 of these awards are made annually.

BRTP also awards approximately 15 Small Grants for Innovative Technology each year for pilot studies in frontline areas of technology research. These studies are characterized by new technological concepts that must be tested and evaluated in small-scale projects before larger funds can be committed.

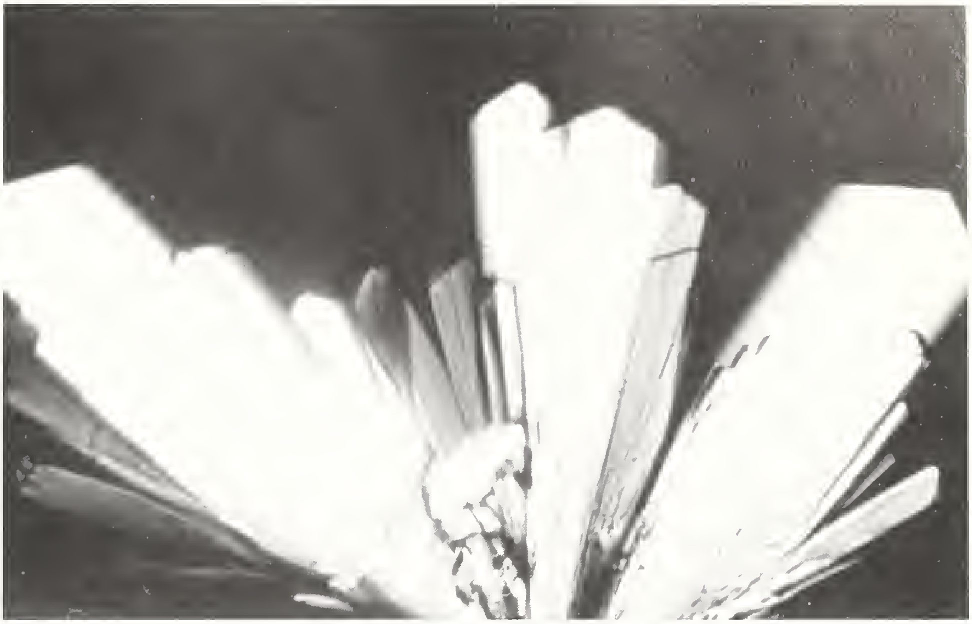
Communication with the biomedical research community is an important part of the BRTP objectives. Through publications, seminars, workshops, and conferences BRTP grantees disseminate research achievements and announce training opportunities in the resource centers and the availability of technical information.

Research Highlights

Perhaps the most rapidly developing frontier in biology is the area of science called structural biology, a field that relates the structure of large molecules such as proteins, nucleic acids, and carbohydrates to their biological function. For example, a key element in a protein's ability to function properly is its three-dimensional shape, which is determined by the folding of its amino acid chains. A protein's activity is also determined by the presence of appropriate sites on its surface for interaction with other molecules; for many proteins these sites of interaction and attachment have been identified as clefts or gaps in the surface structure.

Once a molecular site of interaction has been defined, scientists often attempt to modify it to weaken or strengthen the biological activity of the molecule. Other research efforts may be directed at designing or modifying drugs that fit into particular clefts in the protein molecule. Drugs that are designed to interact with a particular site on a protein are often more specific and thus more powerful than those found by trial and error.

Advanced computer graphics is an essential tool in studies of molecular structure. This



The technique for growing crystals for x-ray crystallography of proteins and viruses has improved in recent years, but it is still often more art than science. It may take years to learn to grow large protein crystals like the ones shown here or, by a stroke of luck, an investigator might succeed in one try.

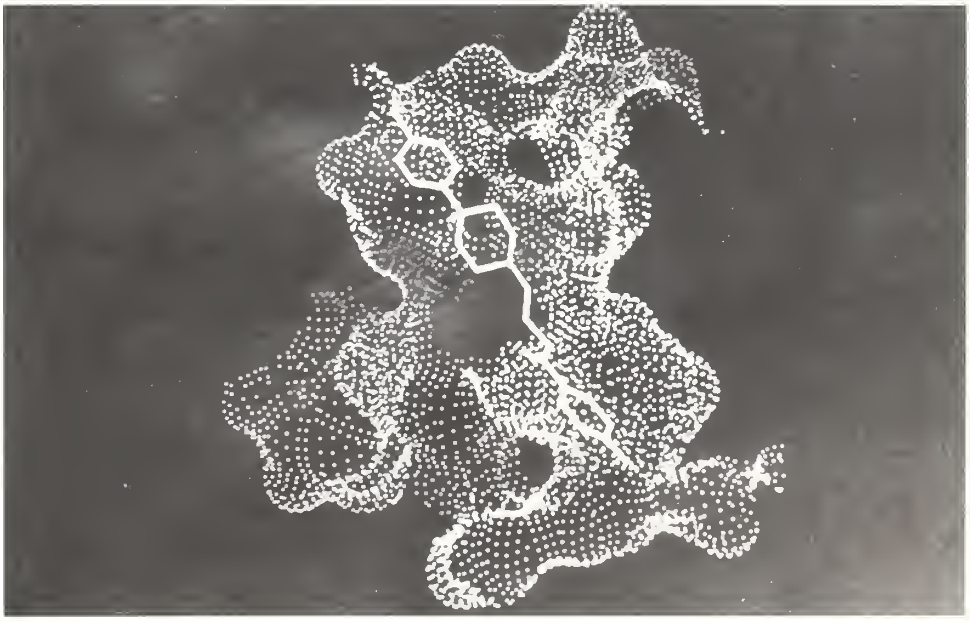
Dr. Alexander McPherson, University of California-Riverside

technology permits the detailed structure of a molecule to be displayed on a computer screen from any desired angle. The sites of molecular interaction may thereby be located and their three-dimensional shapes visualized. Old drugs are being modified and new ones designed with the help of computer graphics to make their shape fit particular interaction sites on proteins.

One of the most important technologies used in structural biology is x-ray crystallography. With this technique the structure of a molecule is determined by analyzing the diffraction of X rays from crystals of the material. The field has advanced markedly in the last 15 years due to the availability of highly intense, sharply focused beams of X rays produced in massive electron storage rings known as synchrotrons and because of the development of advanced computer programs for dealing with the vast quantities of data generated in an x-ray diffraction experiment.

The combination of x-ray crystallography and computer graphics technology is indispensable for understanding the relationship between molecular structure and biological function. A recent significant achievement in this area is the identification of a potential anti-AIDS drug.

Drug Identified by Computer Program Impairs AIDS Virus. Scientists at the University of California, San Francisco (UCSF), using a BRTP-funded resource for structural biology and image analysis, have discovered that the antipsychotic drug haloperidol has structural fea-



In a computer search for potential anti-AIDS drugs at the University of California at San Francisco, the psychoactive drug haloperidol was found to fit snugly into the structure of an enzyme that is essential for the AIDS virus. The dotted outline indicates the three-dimensional structure of the enzyme; the solid-line structure depicts haloperidol. A computer graphics program called DOCK helped investigators identify the drug, but further tests showed that haloperidol would be effective only at a dose level lethal for humans. Scientists are now modifying its structure to reduce toxicity without losing anti-AIDS potential.

Dr. I. Kuntz, Jr., University of California-San Francisco tures that block AIDS virus replication through inhibition of a key enzyme.

The UCSF investigators used an approach known as computer-assisted drug design to compare newly available information about the molecular structure of the key enzyme—a protease essential to replication of the AIDS virus—to the structures of 60,000 chemical compounds in the Cambridge Structural Database, which is made accessible to scientists in the United States by funding from the BRTP.

Stereo images of the HIV protease and candidate drug structures were analyzed by computer; a computer graphics program called DOCK indicated that the haloperidol structure would fit snugly into a cleft or groove on the surface of the HIV protease. Moreover, when the scientists studied the effects of haloperidol in a bacterial cell assay in which bacterial cells mimic HIV-infected cells, they found indications that the drug would block the replication of the AIDS virus.

Although haloperidol itself is not suitable for the treatment of AIDS because of the highly toxic dose levels that would be required, the development of nontoxic chemical relatives of haloperidol is being pursued. The UCSF scientists currently are preparing derivatives of haloperidol that they hope will block the function of the HIV protease, yet could be administered at dose levels that would be safe for persons with AIDS. Much of this work would not be possible without the MIDAS computer graphics software developed at the BRTP-supported molecular graphics laboratory at UCSF. This resource center actively collaborates with the scientists involved in the drug design project.

Stanford, Cornell Synchrotrons Intensify 3-D Images of Molecules. Synchrotron radiation sources provide the most intense and sharply focused beams of X rays available for the study of molecular structures. The BRT Program has played a key part in advancing the technology of x-ray crystallography at synchrotrons at Brookhaven National Laboratory, Cornell University, and Stanford Synchrotron Radiation Laboratory (SSRL). For example, a recent technological breakthrough at Cornell allows scientists to use multiple-wavelength x-ray diffraction to monitor biochemical events as they occur on the surface of a protein.

During 1990 the BRTP-funded resource at SSRL completed its transition to independent operation. Previously, the SSRL was dependent on the Stanford Linear Accelerator for the high-energy electrons needed to generate its x-ray beams. The new arrangement provides SSRL with its own source of electrons, greatly increasing the x-ray beam time available at SSRL. This will help to meet the biomedical research community's high demand for use of the facility. In the last full year of operation outside investigators completed 646 8-hour shifts, which corresponded to 30 percent of the total usage and represented 35 different biomedical projects.

At Cornell University the BRTP has helped to fund research programs under way at the Cornell High Energy Synchrotron Source (CHESS). The CHESS X rays are produced in the Cornell Electron-Positron Storage Ring, or CESR, a one-half-mile ring in which counter-rotating beams of electrons and positrons collide at energies of about 5 billion electron volts. Through windowed ports in the side of the ring scientists can tap into the beam and use its powerful X rays for their crystallographic analyses. CESR X rays are produced in short bursts of about one two-billionth of a second; their brightness and the ultrafast pulses permit the recording of molecular images of fragile biological structures before the crystals are destroyed by radiation.

High-Risk Containment Facility Added to Cornell Synchrotron. The world's first biocontainment facility for synchrotron x-ray crystallography—where crystals of pathogenic materials such as viruses can be prepared and examined safely—was opened at Cornell in June 1990. The $600,000 biological isolation laboratory was designed to meet the high biological safety level-3 standard. Construction was made possible through a cooperative funding effort of the National Center for Research Resources, the National Institute of General Medical Sciences, the National Institute of Allergy and Infectious Diseases, and the National Science Foundation.

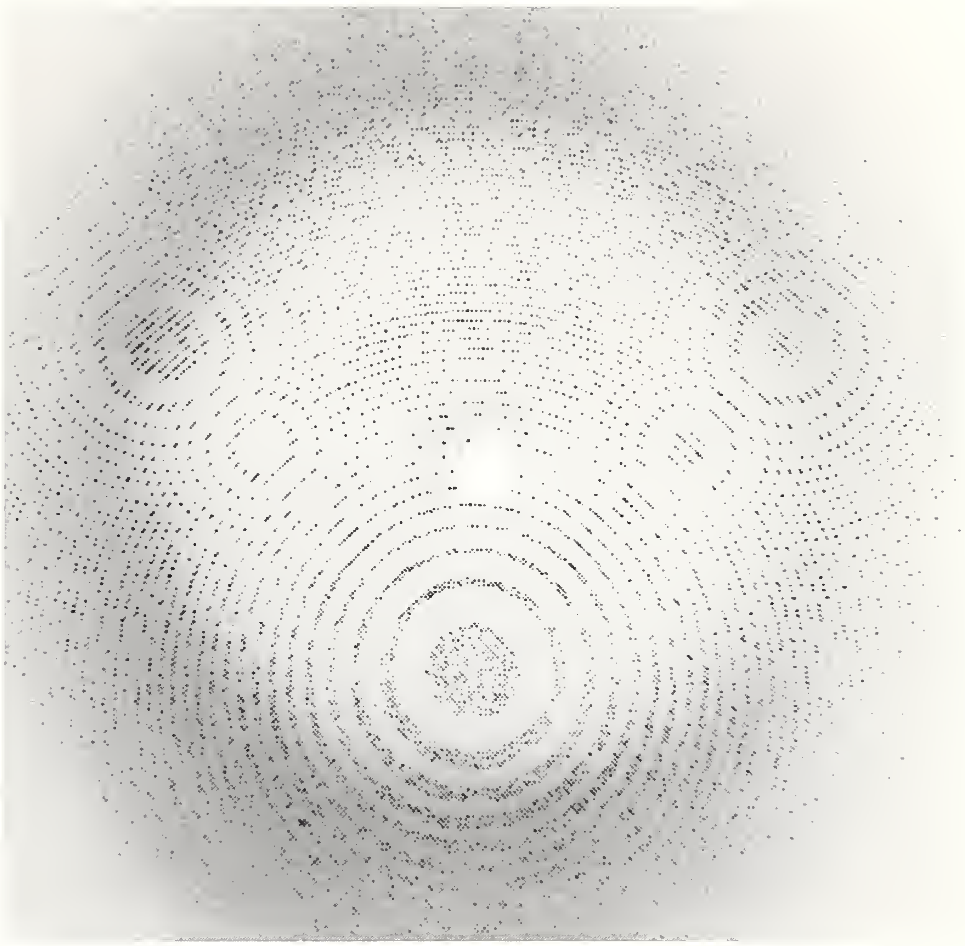
The new facility consists of a self-contained laboratory for preparing viruses and other high-risk biological materials for exposure to the x-ray beam at CHESS. The new addition is part of the NIH-funded MacCHESS program, which permits the use of synchrotron radiation for the study of macromolecular biological structures.

High Voltage EM and Computer Technology Reveal Alzheimer Changes. Alterations in the ultrastructure of nerve cells from the brains of patients with Alzheimer's disease are being illuminated through high-tech neuroscience studies at the University of California School of Medicine in San Diego (UCSD). The researchers employed computer graphics capability provided by the BRT Program, coupled with high voltage electron microscopy, to visualize disruptions that occur inside the brain cells of patients with Alzheimer's disease.

The UCSD scientists have reported preliminary findings of an intensive study of nerve

X-ray diffraction pattern of rhinovirus, the common cold virus. The image was obtained after shining an intense beam of X rays into a crystal of the virus and recording their diffraction on a sensitive film. Information contained in the spacing of the thousands of diffraction spots allowed crystallographers at Purdue University to elucidate the structure of rhinovirus in atomic detail.

Courtesy of Dr. Michael Rossmann, Purdue University



cells obtained from surgical specimens of the brains of patients with early stage Alzheimer's disease. The investigators found that fibrous filaments in the defective Alzheimer neurons had pushed aside the cell's nucleus as well as its Golgi apparatus, which is a special structure inside cells that aids in assembling the carbohydrate side chains of cell proteins. The researchers suggest that the intrusion by the abnormal fibers may cause the neurons to manufacture immature, nonfunctioning proteins.

The discovery was made possible after the investigators prepared a series of high voltage electron micrographs of sections of brain tissue that were only one-hundred-thousandth of an inch thick. Each micrograph showed a slice of a single cell. The investigators traced key structures on an electronic tablet and, using computer imaging technology, assembled the images of the brain cell slices into a three-dimensional image of each cell. These reconstructions, in conjunction with stereo views from high voltage thick-sectioned images, disclosed the unexpected phenomena.

A $3.9 million grant from BRTP has enabled the UCSD researchers to acquire an intermediate voltage electron microscope that, when linked to a supercomputer, will allow them to visualize specimens that are 50 times thicker than those that can be studied with a standard electron microscope. The new microscope will provide clear, detailed three-dimensional images at about half the power of the high voltage electron microscope.

The California investigators believe that extensive research into nerve cells in all stages of Alzheimer's disease is essential for a full understanding of the cellular disruption that occurs in that disease.

Comparative Medicine Program

Program Description

The Animal Resources Program (ARP) was renamed the Comparative Medicine Program (CMP) in late 1990 to express more clearly its mission of providing animal models for human diseases and laboratory animals for biomedical research.

The important contributions of laboratory animals to biomedical research are well known. Almost every advance in the prevention and treatment of important human diseases during the past century has been developed with the use of experimental animals. The Comparative Medicine Program has continued to support a large number and variety of projects related to research animal resources that are essential for investigations of many human diseases.

During FY 1990 the CMP received a total allocation of $67.7 million to provide core support for the seven Regional Primate Research Centers; to upgrade laboratory animal facilities at many biomedical research institutions; to provide diagnostic and laboratory services for colonies of research animals; to train professional personnel to study and care for laboratory animals; to identify and develop new and improved animal models; to breed certain scarce species in order to increase reserves of valuable research animals; to promote the conservation of these species; and to distribute knowledge related to the optimal care and use of laboratory animals.

Approximately $3.1 million was awarded during the year to continue the Chimpanzee Breeding and Research Program that was initiated in September 1986. Chimpanzees are superior animal models for investigations of certain human viral diseases, and their use contributed greatly to the successful development of an effective and safe vaccine against hepatitis B. The chimpanzee is the only animal that can be infected successfully with human immunodeficiency virus (HIV), the causative agent of AIDS. For this reason scientists believe that the chimpanzee is critical to the development of an effective and safe human AIDS vaccine. This breeding program has been extremely successful to date, producing 193 offspring from September 1986 to July 1990.

A specific-pathogen-free (SPF) rhesus monkey breeding and research program that provides monkeys free of certain retroviruses and herpes B virus was initiated in September 1988. The goal is to produce at least 500 SPF rhesus monkey offspring each year for Public Health Service-supported AIDS-related research and other investigations requiring the use of retrovirus-free animals. Six breeding projects and two related research projects (behavioral and genetic) are supported in this effort. The importance of this breeding program for biomedical research is underscored by recent events related to "Ebola-like" disease outbreaks in imported nonhuman primates and the de facto embargo that has been placed on importation of several species of nonhuman primates used in biomedical research.

High quality housing and care must be provided to insure the health and well-being of laboratory animals. In FY 1990 approximately $10.9 million was awarded to upgrade animal facilities and care at institutions throughout the United States. Sanitation equipment, modern caging and runs, and efficient heating/ventilation/air conditioning systems were provided through CMP support awarded to improve environmental quality in these facilities.

Postdoctoral training for graduate veterinarians in the field of laboratory animal medicine continues to be emphasized because of the significant need for specialists in this field. The 17 institutional programs supported by the CMP currently provide specialized training for 69 individuals to ensure high quality management and medical care for laboratory animals. Individual research fellowships and Special Emphasis Research Career Awards (SERCA's) were also granted to graduate veterinarians who are committed to biomedical research careers.

The major areas of the CMP are the Regional Primate Research Centers Program, Laboratory Animal Sciences Program, and the AIDS Animal Models Program, which includes chimpanzee breeding and research and SPF rhesus monkey breeding and research.

The Chimpanzee Breeding and Research Program, which is supported by the National Center for Research Resources, balances the use of chimpanzees for critical scientific studies against the need to preserve these unique, endangered animals for future generations. Animal colonies are strongest when they maintain patterns of behavior associated with life in the wild; here a group of chimpanzees obtains sticky, flavorful, fiber-rich foods by digging with tools such as sticks, much as they dig for termites in the wild.

Courtesy of the Yerkes Regional Primate Research Center

Regional Primate Research Centers Program

The seven Regional Primate Research Centers are a unique network of nonhuman primate research laboratories established between 1960 and 1965 to provide a major scientific resource of regional, national, and international importance to biomedical research. These centers provide for the development and study of nonhuman primate animal models that are essential for clinical and basic research on the mechanisms and processes underlying human diseases and health problems. Because their biological, anatomical, behavioral, and physiological characteristics closely resemble those of humans, nonhuman primates have become an increasingly important resource for biomedical scientists.

The seven centers and the host institutions with which they have close administrative and research relationships are:

- **California Regional Primate Research Center** in Davis, associated with the University of California at Davis;
- **Delta Regional Primate Research Center,** Covington, Louisiana, associated with Tulane University, New Orleans;
- **New England Regional Primate Research Center,** Southborough, Massachusetts, associated with Harvard University, Cambridge;
- **Oregon Regional Primate Research Center, Beaverton,** associated with the Medical Research Foundation of Oregon, Beaverton;
- **Washington Regional Primate Research Center,** Seattle, associated with the University of Washington, Seattle;
- **Wisconsin Regional Primate Research Center,** Madison, associated with the University of Wisconsin, Madison;
- **Yerkes Regional Primate Research Center,** Atlanta, Georgia, associated with Emory University, Atlanta.

These centers provide specialized facilities, nonhuman primate resources, and appropriate research environments for many types of biomedical studies. In 1990 the Comparative Medicine Program awarded approximately $36.4 million to support basic operations and research activities at these centers. This support was complemented by awards for specific research projects from the NIH categorical institutes, other Federal agencies, and private foundations.

Each center has a multidisciplinary group of core biomedical scientists; most of these investigators hold faculty appointments at the center's host academic institution. In addition, hundreds of other biomedical scientists from domestic and foreign research institutions hold collaborative and affiliate research appointments at the regional primate research centers.

The centers help to assure the availability of a wide variety of nonhuman primate species, many of which are now extremely difficult to obtain from their feral sources. The centers have well-equipped laboratories, provide specialized research facilities, and have professional personnel with expertise in the breeding, care, and laboratory use of nonhuman primates. The seven centers collectively maintain over 15,500 primate animals, representing 29 species. Domestic primate breeding programs were established at the centers during the early 1970's to alleviate critical shortages of animals caused by human encroachment on their native habitats throughout the world and by export restrictions imposed by source countries. These breeding programs have been highly successful and have made the centers largely self-sufficient in their supply of primates.

Chimpanzee Breeding and Research Program

The Chimpanzee Breeding and Research Program (CBRP) was established by the Comparative Medicine Program in September 1986 as a multi-institutional program designed to provide a stable supply of healthy chimpanzees for biomedical research and to perpetuate the chimpanzee population in the United States. This is the first and only national program that has brought the expertise and experience of chimpanzee breeders and researchers together for an allied effort. There are currently 450 disease-free adult breeding chimpanzees in the program's colonies, with a total of 193 offspring born since the program's inception. Forty-five percent of these offspring are mother-reared; the remainder are reared with other young chimpanzees in nursery environments. At the present time the CBRP is growing at a rate of 5 percent a year.

Chimpanzees constitute less than 0.1 percent of animals used in biomedical research. However, their unique physiologic and genetic similarities to humans make them the only known natural animal model for some of the most devastating human diseases. For example, the chimpanzee has an important role in research related to two very serious human health threats: hepatitis C and AIDS. Also, because of several naturally occurring cases of leprosy and related amyloidosis, animal model development for the study of these diseases is in progress. Consultants at the National Hansen's Disease Center and the Delta Regional Primate Research Center are assisting in serological testing and epidemiological studies of leprosy among the colony's chimpanzees. Immunology and virology studies to pursue this insidious disease have been initiated. The close immunologic and physiologic similarities of humans and chimpanzees make these animals especially valuable for testing the safety and efficacy of therapeutic drugs produced by new biotechnology techniques. The CBRP receives oversight and advice from a management committee that com-

Dogs help to rear infant chimpanzees at the Primate Foundation of Arizona, a CMP grantee in the Chimpanzee Breeding and Research Program. Dogs serve as surrogate mothers, socializing the infant chimpanzees and also taking the roles of playmate and disciplinarian, as well as grooming the infants and being groomed by them.

Primate Foundation of Arizona

prises facility managers from participating institutions, an ethicist, a zoological park director, and CMP staff. The committee develops standardized policies related to a wide range of issues, including use of chimpanzees in infectious disease research, safety considerations for personnel working with chimpanzees, and environmental enrichment for the captive population. The program has developed significantly, and production is currently stabilized. Offspring from the CBRP can be made available for Public Health Service-sponsored behavioral studies and biomedical research, including studies on AIDS.

Studies on genealogy have produced data showing that a large fraction of the known genetic variation is present in the captive chimpanzee population and that correct breeding techniques minimize the risk of inbreeding.

Research projects integrated into the breeding program are designed to correct gaps in scientific knowledge and problems affecting the reproduction of chimpanzees in captive environments. These studies focus on behavioral development, reproduction, genetics, health, demography, and breeding management. The studies are conducted at the University of Pittsburgh in Pennsylvania; Texas A & M University at College Station; the University of Texas at Bastrop; the Primate Foundation of Arizona in Tempe; Yerkes Regional Primate Research Center in Atlanta, Georgia; and the International Species Inventory System, headquartered in Apple Valley, Minnesota. CBRP companion research studies continue to help achieve the ultimate goals of the program. For example, paternity of most of the animals has been established using genetic mapping techniques, and pedigree lines are being developed from the data. Current phenotypes are being determined, based on discrete genetic loci, that will indicate the level of heterozygosity within the CBRP population. These genetic data will be used to help manage the program and eventually influence the fertility and survival of the captive chimpanzee species. Reproduction and fertility research represents an important extension of the program that can be applied directly to improving reproductive efficiency in the chimpanzee; it will also enhance research on alternatives to natural breeding, e.g., embryo freezing (banking), embryo transfer technology, and induction of multiple births (twinning). The reintegration of chimpanzees into social groups for long-term maintenance is also of primary concern to this program. Progress in socialization at the Primate Foundation in Tempe and the University of Texas at Bastrop has accomplished 221 such chimpanzee reintegrations. With expansion of behavioral-type research almost all captive chimpanzees could be housed safely in compatible social groups.

As scientific problems become more complex it will become even more evident that animal models such as chimpanzees continue to have an important role in human health-related studies. When chimpanzees are employed as the research model of choice every effort is made to ensure that they are used in the most humane and appropriate manner. Chimpanzees from the CBRP may be assigned to U. S. Public Health Service or other government-supported research projects, pending approval of the research protocols by the Interagency Animal Models Committee. This review is in addition to prior evaluations of the individual protocols by institutional animal care and use committees and the particular funding agency's peer review system.

Specific-Pathogen-Free Rhesus Breeding and Research Program

The Specific-Pathogen-Free Rhesus Breeding and Research Program was established by CMP in September 1988 to create self-sustaining rhesus breeding colonies that are free of simian retroviruses and herpes B virus. This is the first national effort to ensure the development of a stable population of SPF rhesus monkeys. In addition to making SPF animals available to Public Health Service-supported research projects related to AIDS, the program promotes research to enhance the quality of well-defined animals through the development of modern diagnostic tests for retroviruses and herpes B infection; improved housing and husbandry practices; computerized record systems; and new techniques that permit indepth genetic monitoring.

Nonhuman primates, particularly SPF rhesus monkeys, continue to be the most consistent and widely used animal model for AIDS research. To fulfill the critical need for SPF rhesus monkeys in research on vaccine development and drug therapy for AIDS, SPF rhesus breeding colonies have been established at these locations: Texas Primate Center of Hazleton Research Products in Alice, Texas; New England Regional Primate Research Center in Southborough, Massachusetts; University of Texas in Bastrop; the Michigan Department of Public Health in Lansing; Laboratory Animal Breeders Service in Yemasee, South Carolina; and the University of Miami School of Medicine in collaboration with Charles River Laboratories, Key Lois, Florida. A management committee provides oversight and guidance for the overall production strategy. This committee includes breeding facility managers, principal investigators, and CMP staff. The committee is responsible for the development and implementation of standards for health, population demographics, and computerized record and tracking systems that can be readily shared to benefit the entire SPF program.

Ebola-like viruses represent a serious threat to SPF rhesus colonies. A major aspect of the SPF effort is the development and application of viral surveillance programs against these and other viruses to assure that the SPF status of the colonies is constantly maintained. Continued selection of progeny for future breeding and assurance of maximal genetic diversity in the colonies are also of high priority. Although the precise number and characteristics of SPF rhesus monkeys needed for retrovirology research cannot be predicted, an adequate and dependable source of high quality SPF rhesus monkeys is absolutely essential for future AIDS-related investigations.

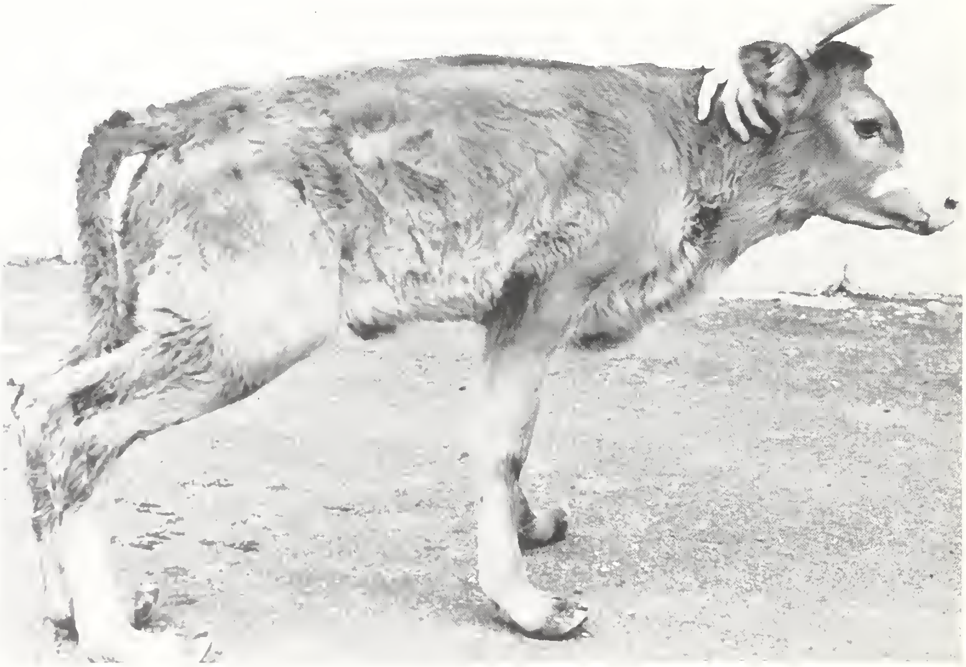
Laboratory Animal Sciences Program

Activities supported by the Laboratory Animal Sciences Program (LASP) have continued to focus on improving the well-being of laboratory animals, investigating the cause and spread of diseases, and developing appropriate control measures. Studies include the identification, characterization, and development of new animal models for use in biomedical research. As examples, dogs, mink, and cats naturally develop an inherited disease that causes defective collagen formation; horses develop a genetic immunodeficiency; dogs and mice develop diabetes; and a certain rat strain spontaneously develops high blood pressure. Postdoctoral training in laboratory animal medicine is also an area of emphasis. Specifically, the LASP seeks to:

- Develop improved methods for the diagnosis and control of laboratory animal diseases;
- Support breeding colonies to ensure the availability of adequate supplies of animals needed for research on human diseases;
- Provide assistance for institutional animal resource improvement projects to upgrade animal facilities and develop centralized programs for high quality animal care;
- Train graduate veterinarians in the specialty of laboratory animal medicine; and
- Support the distribution of information related to animal research, sources of laboratory animals, and biological specimens.

The LASP budget totaled approximately $31.3 million in FY 1990. A summary of each element of the program is provided below.

Institutional Animal Facility Improvements. Healthy research animals are necessary if the data derived from their use are to be valid and reproducible. The housing and care of these animals must be optimal and infectious diseases must be eliminated. To assist institutions in their efforts to meet the animal care guidelines established by the Public Health Service and the requirements of the Animal Welfare Act, the LASP has continued to support projects to improve institutional animal facilities. Of the 119 animal resource improvement applications received for FY 1990, 51 were funded at a total of approximate-



Investigators at Washington State University in Pullman have identified a bovine model of the Marfan syndrome, a hereditary life-threatening connective tissue disorder. This calf has abnormally long, thin hind legs and severe joint and tendon laxity. Marfan syndrome in humans is associated with similar defects.

Drs. K. Potter and T. E. Besser, Washington State University

Curator Dr. Jean Turnquist at the Caribbean Primate Research Center Museum in San Juan, Puerto Rico, examines skull bones from one of the approximately 2,000 monkey skeletons in the CMP-funded collection.

Dr. Jean Turnquist

ly $10.9 million. This support was used to renovate existing animal facilities, improve the environment and overall quality of animal resources, upgrade animal caging, and improve sanitation by providing equipment such as cage washers and autoclaves.

Training and Career Development. The shortage of veterinarians well trained in the specialty of laboratory animal medicine continues to be an important issue. In FY 1990 the LASP supported the training of 69 veterinarians via 17 institutional programs and of 3 veterinarians through individual postdoctoral fellowships. These programs are designed to prepare individuals for careers in laboratory animal medicine and science.

The LASP also continued to support the Special Emphasis Research Career Award Program. SERCA awards are made to veterinarians to enhance their development in biomedical research careers involving the use of laboratory animals. The award provides support for 5 years and is designed to provide the training necessary for the awardee to become an independent investigator.

Diagnostic and Investigative Laboratories. The major objective of the diagnostic and investigative laboratories is to improve laboratory animal health and enhance biomedical research at large medical research institutions. This is accomplished through the control of naturally occurring diseases, studies of the etiology and pathogenesis of laboratory animal diseases, detection and characterization of new diseases, and the development of new or improved animal models of human disease. Animals with unique susceptibility to disease, including transgenic and immunodeficient animals, are of great value in biomedical research.

Animal Models and Special Colonies. Bacteria- and virus-induced infectious diseases, endocrine abnormalities, inherited metabolic imbalances, and tumors are among the maladies that affect both animals and humans. Consequently, animals often provide excellent model systems for the study of diseases that afflict humans.

In FY 1990 CMP supported seven animal model and special colony projects. These projects were devoted to identifying new models of human disease, improving the characterization of some already identified models, and increasing the availability of animal stocks that have proved useful to biomedical researchers but are not available from commercial sources.

Animal models that have been helpful in the study of the etiology, pathogenesis, and treatment of human infectious, genetic, and malignant diseases include a wide variety of species. The detection of new models requires that the naturally occurring diseases of a wide variety of species be closely monitored. Investigators in LASP-sponsored programs have studied numerous diseases of rodents, rabbits, cats, dogs, cattle, and nonhuman primates. Another program has focused on the characterization of the ferret, an animal that is becoming highly useful as a model for studying human gastrointestinal infections and other problems. To help ensure the availability of an important but unusual laboratory animal, CMP also supported studies on colonies of woodchucks.

Nonhuman Primate Resources. The LASP supported several projects dealing with the breeding, genetic characterization, diseases, and laboratory environment of nonhuman primates. The Caribbean Primate Research Center (CPRC) of the University of Puerto Rico Medical Sciences Campus has a unique free-ranging rhesus monkey colony on Cayo Santiago, the Sabana Seca Field Station, and a skeletal collection. The major areas of research are social behavior; demography and population genetics; endocrinology; spontaneous diseases such as diabetes mellitus, macular degeneration, arthritis, and hypertension; and functional morphology of nonhuman primates.

The Cayo Santiago colony is also an important source of healthy monkeys for AIDS-related research. Since 1956 maternal genealogical and demographic data have been collected continuously on the free-ranging rhesus colony. This has resulted in the most complete life-history data base on any nonhuman primate population in the world. The CPRC's skeletal collection also maintains 1,600 complete or nearly complete skeletons of 11 species of Old and New World primates. Approximately 900 of the skeletons are of known identity, age, sex, maternal lineage, social group, diet, and reproductive history.

A colony supported at the University of South Alabama has become the largest breeding colony of squirrel monkeys in the United States. Behavioral, biochemical, and cytogenetic studies are being conducted to improve the reproductive efficiency of the colony and to characterize the squirrel monkey as an animal model.

The genetic management of nonhuman primates to accurately identify parents and avoid inbreeding is becoming increasingly important as greater emphasis continues to be placed on developing self-sustaining colonies of nonhuman primates for biomedical research use. In addition to studies aimed at genetic characterization and colony management, several behavioral studies to evaluate and determine methods of enhancing the well-being of nonhuman primates used in research were initiated during FY 1990.

Reference Centers. The LASP supports two centers that collect tissues and other biological specimens from laboratory, domestic, and wild animals to provide reference material for investigators. The Registry of Comparative Pathology of the Armed Forces Institute of Pathology in Washington, D.C., maintains a collection of tissues and illustrative material that is available for research and research training. It also conducts workshops, symposia, and short courses; prepares study sets and syllabi for loan; and provides investigators with expert consultation on comparative pathology. The other center is the Facility for Cryopreservation of Murine Germplasm at the Jackson Laboratory in Bar Harbor, Maine. This center has pioneered the techniques used for freezing mouse embryos to preserve valuable strains that may be needed for research in the future. The approach permits a reduction in the number of live animals that must be maintained and helps to maintain the integrity of the inbred animals.

Other reference centers supported are primarily of an informational nature. The Institute of Laboratory Animal Resources of the National Research Council, with the support of LASP and other government agencies, provides scientific and technical information about laboratory animal resources. It also develops guidelines on laboratory animal care and use and conducts workshops on laboratory animal problems. Several thousand copies of the resulting Proceedings are distributed to the scientific community each year. The Laboratory Primate Newsletter published by Brown University in Providence, Rhode Island, and the New Listings from the Primate Supply Information Clearinghouse at the University of Washington in Seattle provide important information regarding the care, breeding, and supply of nonhuman primates for biomedical research.

Research Highlights

Regional Primate Research Centers

Research to Prevent Hemorrhagic Shock Damage in Trauma Victims. Scientists at the Washington Regional Primate Research Center have described the results of a study in rhesus macaques that may benefit many of the 50,000 American trauma victims who develop multiple organ damage each year following accidents and other injuries.

In the Washington studies a new approach using monoclonal antibody targeted to white blood cells called polymorphonuclear neutrophils (PMN's) prevented PMN adherence and aggregation in five hypotensive monkeys treated with the antibody after they had been in hemorrhagic shock for 90 minutes. Given at the time of resuscitation, the monoclonal antibody MAb 60.3 reduced fluid requirements and gastric injury in treated animals. They recovered with less intensive therapy than did control animals and showed none of the organ damage seen in controls.

The approach was developed by the Washington investigators after they had hypothesized that fatal damage to the digestive tract, lungs, or other organs far from the site of a traumatic injury often does not occur during the injury and resulting shock, but in the first minutes after normal blood pressure is reestablished.

It is expected that this promising new procedure may be assessed within the coming year in persons with life-threatening shock due to traumatic injury.

Induction of AIDS by Molecularly Cloned Virus. Investigators at the New England and California Regional Primate Research Centers have demonstrated for the first time that molecularly cloned simian immunodeficiency virus (SIV) can induce in common rhesus monkeys a disease remarkably similar to human AIDS. Disease induction has not been reported previously for any molecularly cloned lentivirus. The results provide another strong link in the chain of evidence for the viral etiology of AIDS. More importantly, they define a system for molecular dissection of the determinants of AIDS pathogenesis that will be useful for drug development and for AIDS vaccine studies.

AIDS Vaccine Research and Successful Studies in Monkeys. During the past year scientists at the Delta and New England Regional Primate Research Centers demonstrated independently that it may be possible to develop an effective AIDS vaccine. Investigators at the New England center reported that protection from SIV, a nonhuman primate virus that is very similar to human immunodeficiency virus (HIV), was achieved in two of six monkeys using a whole virus vaccine preparation. Later in the year a team of investigators at the Delta center developed a prototype AIDS vaccine using the SIV/Delta isolate that infects rhesus monkeys. The vaccine succeeded in preventing eight of nine exposed animals from developing AIDS. This vaccine strategy used in nonhuman primates may serve as the basis for development of an AIDS vaccine for human populations at risk of infection.

Language Acquisition in Chimpanzees. Through comparative research, a team of investigators at the Yerkes Regional Primate Research Center has completed studies aimed at

To help alinguistic humans acquire communication skills scientists at the Yerkes Regional Primate Research Center in Atlanta, Georgia, are studying language development in chimpanzees. Nine-year-old Kanzi is able to comprehend sentences composed of the symbols on the boards.

Language Research Center, Georgia State University/ Yerkes Regional Primate Research Center

improving our understanding of the processes underlying language development. The studies were designed so that what is learned might be applied toward intervention for alinguistic humans. During the past year the investigators focused principally on testing sentence comprehension in their most sophisticated symbol-using chimpanzee Kanzi, a 9-year-old bonobo (Pan paniscus). Data were also collected on an alinguistic human subject 23 months old.

Complex and novel English sentences were presented to both subjects under carefully controlled, blinded conditions. A total of 728 sentences were presented to Kanzi; 698 sentences were presented to the child. Results revealed comprehension of similar forms of syntax, with similar errors, by the ape and the child.

Steroid Hormones and Fetal Development. Researchers at the Oregon Regional Primate Research Center are studying the actions of steroid hormones on sexual differentiation of the nonhuman primate brain and peripheral tissues. Studies to date have focused on androgens such as testosterone (T) and dihydrotestosterone (DHT), which are normally secreted by the fetal testes during a critical developmental period. Previous experiments at the center have shown that high affinity androgen receptors are found in the brain and the pituitary; the investigators have also shown that high affinity receptors are found in the developing heart, spinal cord, reproductive tract, liver, and kidney. The Oregon scientists now propose that prenatal androgens are important for the differentiation of many other tissues in addition to those in the brain and reproductive tract.

Previous studies failed to show a nuclear androgen receptor in the brain or pituitary gland of the fetal monkey. However, the Oregon team recently injected exogenous DHT into late gestation fetuses and found that the nuclear receptor could be quantified. The data suggest that the androgen receptor in the fetus can be activated and provide additional proof that these receptors are functional.

Receptor Differences in Male and Female Fetal Monkey Brains. Androgen receptors are differentially distributed between the right and left brain hemispheres of the fetal male rhesus monkey, according to a 1990 study by scientists of the Wisconsin Regional Primate Research Center in Madison.

In studies of five male and six female monkey fetuses they found that androgen receptor levels in the right frontal lobe of every male fetal brain studied were higher than in the left frontal lobe. In contrast, a consistently higher level of androgen receptors was found in the male's left temporal lobe than in the right lobe.

In female fetuses there was no consistent pattern in the distribution of the receptor between the two sides of either the frontal lobes or the temporal lobes.

The scientists believe that the differences they observed lend support to the hypothesis that prenatal androgens may influence cortical activity of the brain.

Regional Primate Research Centers AIDS Conferences. Communications among researchers studying AIDS in nonhuman primates have improved significantly since initiation of CMP-funded Annual Symposia on Nonhuman Primate Models for AIDS. The meeting has grown from a small informal workshop in 1983 to a major annual conference with more than 200 scientists attending; it is sponsored annually by one of the seven regional primate research centers.

The conferences have advanced the progress of several highly important areas of AIDS research, in particular the development of promising candidate vaccines against AIDS. In 1990 the symposium, sponsored by the Delta Regional Primate Research Center, was held in New Orleans, Louisiana.

Laboratory Animal Sciences Program

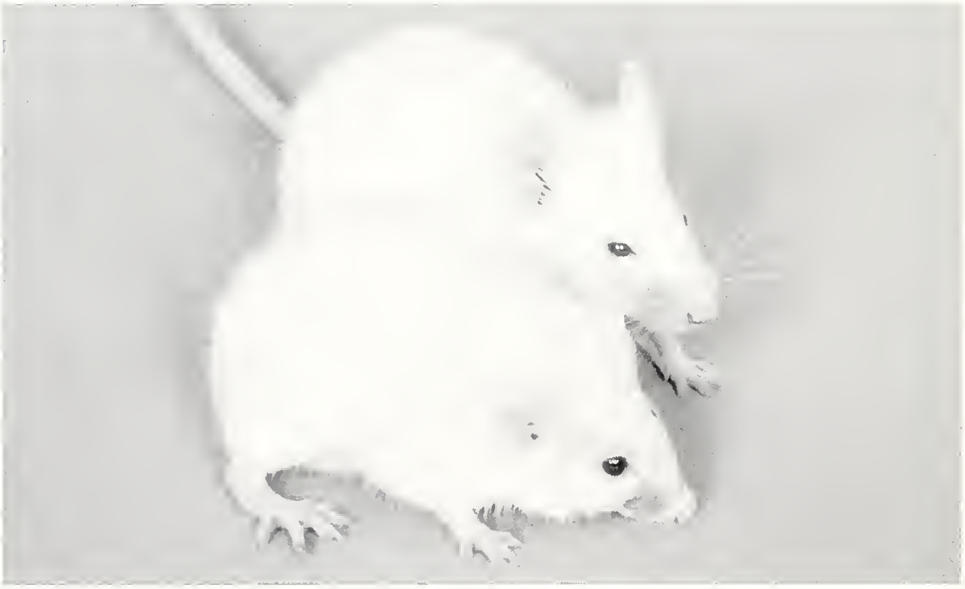
An Animal Model for Cryptosporidiosis. Cryptosporidiosis is a protozoal infection of the small intestine of humans and animals. Up to 30 percent of AIDS patients are diagnosed with this opportunistic pathogen; infections are often fatal since no effective drug therapy is available. Cryptosporidiosis is also a major cause of diarrhea among children. Until now there was no reliable small animal model for spontaneous cryptosporidiosis available to biomedical researchers.

The disease was diagnosed in guinea pigs with diarrhea by investigators at the University of Michigan's Laboratory Animal Diagnostic Laboratory; occasional deaths were observed. The LASP-funded scientists have experimentally transmitted the disease by oral inoculation of oocysts to both juvenile and adult guinea pigs. They found that guinea pigs could become infected by fewer than 350 oocysts. Examinations at weekly intervals after inoculation showed recovery from the disease by 4 weeks of age. The scientists reported in 1990 that the recovered animals were completely resistant to challenge by reinoculation.

Currently, the investigators are trying to use the model to study mucosal immunity to cryptosporidiosis. Results may lead to strategies for immunotherapy of AIDS patients with this opportunistic infection and perhaps to an effective vaccine for prevention of cryptosporidiosis in children.

SCID Mouse Model for Studying Life-Threatening Pneumonia. The severe pneumonia caused by *Pneumocystis carinii* (Pc) creates an important health problem in immunocompromised individuals, especially in patients with clinically evident acquired immunodeficiency syndrome who are coinfected with cytomegalovirus (CMV). This suggests the possibility that other infections may somehow enhance the development of pneumocystosis. Investigators at the Laboratory Animal Diagnostic Laboratory at Yale University School of Medicine in New Haven, Connecticut, found that mice with severe combined immunodeficiency (SCID), which are mutant animals with virtually no antigen-specific lymphocytes or immune function, developed fulminant Pc infection after they were moved from a barrier facility into a conventional research colony.

One hypothesis is that an infectious agent, *Pasteurella pneumotropica*, present in the research colony and absent from the barrier facility, enhanced the development of pneumocystosis. *P. pneumotropica* produced an infection that was clinically silent until about 2 months after infection. An analysis of pulmonary tissue of the mice demonstrated a significant increase of Pc cysts in infected mice.



Mice with severe combined immunodeficiency, a genetic disease characterized by defective immune defenses, have been adapted to serve as a small animal model for infection by human immunodeficiency virus.

Stanton K. Short, The Jackson Laboratory

Immunotherapy and Radiotherapy of Mice With Lymphomas. At the LASP-supported division of laboratory animal medicine at Stanford University School of Medicine in Stanford, California, mice with lymphoma—cancer of the lymph nodes and other immune system organs—have been studied as a model for the human disease.

A new treatment strategy consists of making custom antibodies to a patient's tumor cells and injecting these antibodies into the patient to destroy the tumor. Much developmental work done at Stanford University has been performed using lymphoma-bearing mice. Since the custom-made antibodies are by themselves only marginally effective, methods are being sought to increase their usefulness by tagging them with drugs or radioactive compounds.

In lymphoma-bearing mice, as in some patients with lymphoma, tumors might be eliminated but the aftereffects of therapy were sometimes fatal. The LASP-supported scientists have been attempting to develop methods to prevent the crucial side effects of high-dose radiation. Laboratory studies and postmortem examinations of the radiation-treated mice indicated that most mice—like patients with similar tumors—die from infection or uncontrolled bleeding in the brain or other vital organs. The studies in animals have shown that the radiation dose rate, total body dose of radiation, and microscopic effects in the vicinity of the tumor are all critical to the outcome.

Campylobacter and Gastric Disease in Ferrets. Gastric ulcers and gastritis have frequently been diagnosed in various species of animals, including ferrets. The latter is of particular interest since the ferret stomach shares many anatomic and physiologic features with the human stomach.

Investigators at the research animal diagnostic laboratory of the Massachusetts Institute of Technology recently isolated *Campylobacter*-like organisms (CLO) from gastric lesions in ferrets as well as from normal gastric tissue of ferrets. Electron microscopy showed that in ferrets with gastritis the organisms were associated with the minute projections called microvilli on the epithelial layer of the stomach; occasionally the organisms were found inside the epithelial cells. The organism was isolated and termed *Campylobacter mustelae.* It has many biochemical and morphological features in common with *Campylobacter pylori,* which is associated with human gastritis. Further studies are now under way, with support from the NIH and private industry, to establish the usefulness of the ferret model in studying CLO pathogenesis.

Biomedical Research Support Program

Program Description

The Biomedical Research Support Program (BRSP) of the National Center for Research Resources provides three unique grant programs designed to help federally supported institutions meet critical research needs. These programs, which promote innovation in the biomedical sciences, strengthen research infrastructure, and provide precollege research experience, include: the Biomedical Research Support Grant (BRSG) Program, the Shared Instrumentation Grant (SIG) Program, and the Minority High School Student Research Apprentice (MHSSRA) Program. Institutions receiving such support include graduate schools, health professional schools (medicine, dentistry, pharmacy, veterinary medicine, and nursing), not-for-profit research organizations, and hospitals.

In FY 1990 appropriations for the three grant programs totaled $78.8 million.

The Biomedical Research Support Grant Program

The BRSG Program provides flexible funds on a formula basis to institutions to support biomedical research needs that are not met by other NIH research grant programs. Grantees are permitted flexibility in determining where and how funds are applied to provide short-term, low-cost, interim, and shared resource needs. As sources of other research funds are reduced or eliminated the BRSG has played an increasingly important role in the support of research programs.

To be eligible for support from the BRSG Program an institution must have received at least three Public Health Service research grants totaling $200,000 or more during the previous Federal fiscal year. The size of a BRSG grant is calculated by applying a formula to the institution's previous year level of PHS-supported research. A total of 629 institutions received $44.3 million in BRSG awards in FY 1990, the largest of which was $260,396 awarded to Johns Hopkins School of Medicine in Baltimore, Maryland; the smallest was $4,513 awarded to the University of New Orleans in Louisiana. Examples of high-priority research needs not met by project-oriented research grants include:

- ***Pilot Studies.*** The BRSG Program is widely recognized as a prime source of support for new, novel, and innovative research ideas in the early stages of development. In FY 1990 the BRSG Program supported more than 8,000 pilot and other research projects at an average cost of less than $5,000 per project. The projects covered such high interest areas as Alzheimer's disease and other age-related diseases, AIDS, drug addiction, and women's health issues, including breast cancer, osteoporosis, and prenatal alcohol exposure.
- ***Young Investigators.*** BRSG funds aid newly recruited faculty members in establishing their laboratories and provide seed money to help them develop competitive extramural grant applications. More than 220 investigators who received BRSG funding in FY 1988 and 1989 were subsequently awarded 5-year FIRST (First Independent Research Support and Transition) awards totaling $19.6 million. Recipients of BRSG awards in those 2 years later garnered 18 percent of the new regular research grants (RO1's) awarded by the NIH.
- ***Interim Support.*** Sharp reductions in the number of new and competing NIH research grants have had a detrimental effect on many competitive renewal applications despite excellent priority scores or percentile rankings. Increasing numbers of these meritorious projects have been supported with BRSG funds on an interim basis, keeping productive programs alive during temporary breaks in funding and preventing expensive shutdown and startup procedures.
- ***Central Research Facilities.*** As the funding climate at the national level becomes more restrictive, BRSG funds are called upon to support core facilities such as recombinant DNA and cloning facilities or high containment cell culture and hybridoma laboratories, as well as to upgrade animal facilities to achieve compliance with animal welfare regulations.

The program provides no indirect costs and for low-cost projects decentralizes research support decisions that need not be made by NIH staff, which allows biomedical research to proceed in a highly economical manner with a major saving of time, money, and overhead expenses.

The Shared Instrumentation Grant Program

Sophisticated, complex instrumentation has played a critical role in extending the boundaries of scientific frontiers. It makes new experiments possible, providing new information and opening up new areas of basic and clinical research. It increases the rate at which new knowledge can be obtained because data can be accumulated and analyzed faster. It increases the sensitivity of measuring techniques, making data more reliable. The enormous increases in instrumentation capability also come at an increased cost. Today's elaborate instrumentation is so expensive that it must be shared among many investigators. The Shared Instrumentation Grant Program provides very expensive instruments to groups of PHS-supported investigators to enhance their current programs and to provide the tools to conduct modern biomedical research. SIG awards provide instrumentation in the $100,000 to $400,000 cost range for routine instruments such as electron microscopes; cell sorters; and DNA sequencers; as well as state-of-the-art, powerful, new nuclear magnetic resonance imagers; coupled hybrid mass spectrometers; and scanning laser confocal microscopes.

In FY 1990 the program received 403 applications, an increase of approximately 35 percent from FY 1988. Of these, 144 applications, 6 fewer than in FY 1989, were funded for a total cost of $32 million.

Minority High School Student Research Apprentice Program

The long-range goal of the MHSSRA Program is to increase the number of minorities in health-related research or the health professions. Changing demographics predict that more minority representation will be needed in the health care professions, both on the level of the health science researcher and the level of the practicing physician. In addition, improving the health status of minority Americans requires culturally sensitive and ethnically acceptable programs designed by minority health professionals.

The MHSSRA Program is the only NIH program aimed at attracting precollege minority students to careers in science. The program plays an integral role in exciting interest in and motivating the pursuit of science by providing minority high school students with up to 8 weeks of hands-on experience in basic and clinical laboratories. Learning the basic concepts of molecular and cell biology, evolution, heredity, development and reproduction, and ecology by carrying out genuine investigations helps promote an interest, curiosity, and understanding of scientific concepts beyond the textbook and classroom experience.

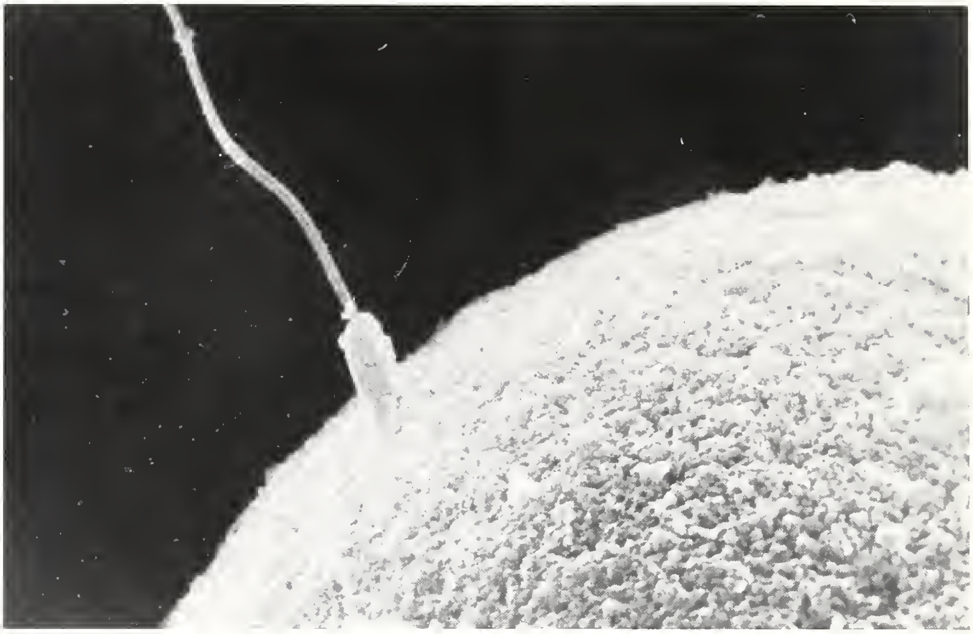
In FY 1990 the MHSSRA Program awarded $3.2 million to 358 major research and training institutions that were responsible for recruiting and assigning students to experienced and sensitive mentors. More than 2,150 science-oriented students participated in the program in 1990—a 93-percent increase over the 1,116 students who participated in FY 1989. The MHSSRA Program supported 1,406 of these apprentices. An additional 746 students were supported by $1.2 million from other NIH institutes, centers, and divisions as well as from the Alcohol, Drug Abuse and Mental Health Administration, which brought the total funding to $3.2 million.

The MHSSRA Program began in FY 1980 with $400,000, which provided for only 200 student positions. In subsequent years more than 10,000 students have participated in the MHSSRA Program. The program is reaching different minority groups: 55 percent of the students are black, 17 percent Hispanic, 22 percent Asian, 3 percent Native Americans, and 3 percent are other ethnic minorities. Female students held 60 percent of the apprenticeships in FY 1990.

Research Highlights

Greater Fertility of Genetically Dissimilar Mates. Studies of the Hutterites, an inbred and highly fertile population of European ancestry living in the United States and Canada, indicate that fewer successful pregnancies occur when a husband and wife share one or more human leukocyte antigens (HLA), immunologic markers situated on the surface of cells. Findings by the University of Chicago investigators who conducted this BRSG-supported study reinforce the concept that genetic dissimilarities between mates may increase the chances of successful reproduction.

At the outset of the study, BRSG funds were used to finance field trips to widely scattered Hutterite communities and to collect and ship blood specimens to the University of Chicago in Illinois where the samples were evaluated. Preliminary findings were suffi-



The success of a pregnancy may be determined by the genetic dissimilarity of parents, according to University of Chicago BRSP grantees. A successful pregnancy begins with penetration of a sperm into an egg to create a new individual with characteristics inherited from both parents.

Courtesy of Dr. D. W. Fawcett and Dr. E. Anderson, Harvard Medical School

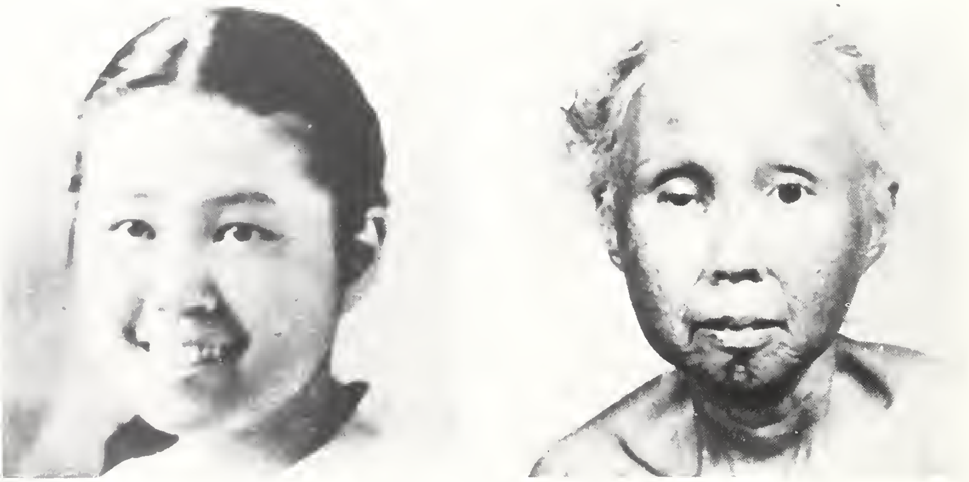
ciently promising that the National Institute of Child Health and Human Development awarded grant funds to continue the research.

Results of the research now indicate that of 111 Hutterite couples, those sharing one or more HLA antigens had longer intervals from marriage to the birth of a child than did couples who did not have HLA genes in common. Furthermore, the investigators found that one genetic locus in particular, the HLA-DR locus, seemed to have the greatest impact on the Hutterites' fertility.

The Chicago investigators are now initiating a large-scale study to characterize the HLA of fetuses of couples in the general population who have experienced recurrent spontaneous abortions to assess whether the Hutterite data may apply to the population at large.

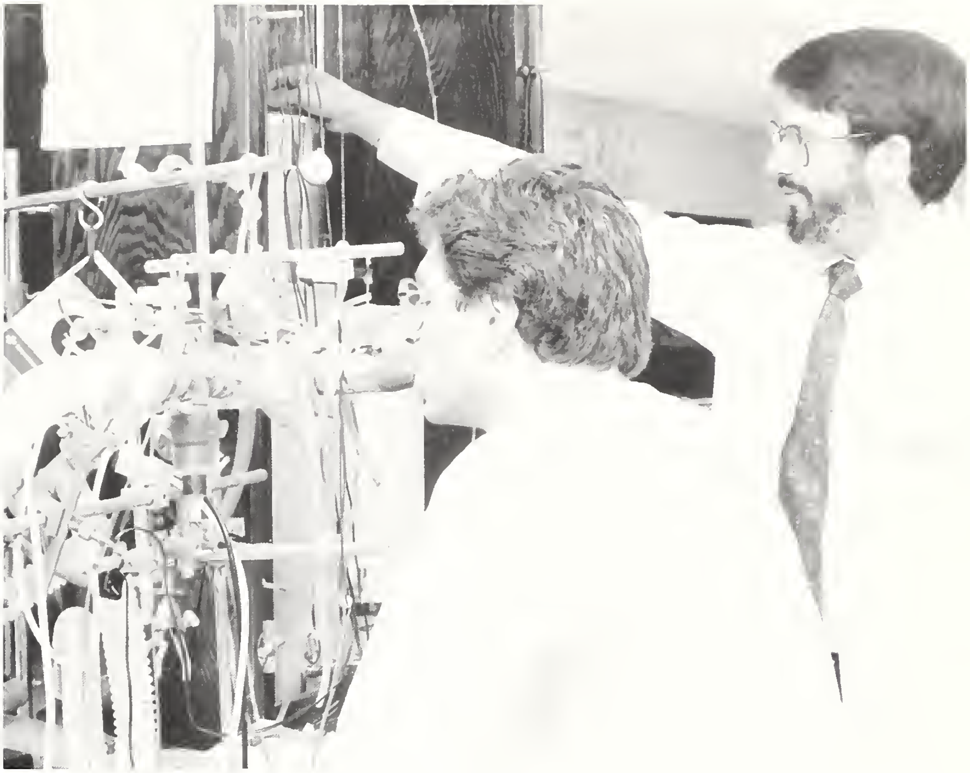
A Disease of Premature Aging Is Studied. A BRSG award that provided startup funds for a cell culture laboratory at the University of Washington in Seattle is contributing new information about a rare genetic disease of premature aging called Werner's syndrome (WS). The disease produces cataracts, grey hair and baldness, osteoporosis, and other age-related conditions among affected persons during their twenties and thirties. By studying cultured cells from WS patients, the Seattle scientists learned that the patients had inherited a genetic mutation that affects an enzyme known as HPRT that contributes to the synthesis of DNA. To determine the molecular nature of the gene aberration, the scientists isolated chromosomal DNA from WS cell cultures and in a series of molecular biology maneuvers contrasted it with normal chromosomal DNA.

They found that 76 percent of the DNA from WS cells, which show signs of accelerated aging even as they grow in the laboratory, lacked segments of DNA at the HPRT locus. Only 39 percent of normal cells had comparable deletions of DNA.



Werner syndrome, a rare inherited disease of premature aging, is being studied by a BRSP grantee at the University of Washington, Seattle. The patient in these photos is shown as a teenager and at 48 years of age.

Courtesy of Dr. G. M. Martin, Williams and Wilkins Co., and Springer Verlag



The rigidity that affects leg muscles of Parkinson's disease patients may also inhibit respiratory muscle function and create problems in breathing, according to a BRSP-supported study at Brown University in Providence, Rhode Island. Dr. F. Dennis McCool (right) evaluates the respiratory muscle strength of a healthy volunteer.

Dr. F. D. McCool

One of the investigators working on the BRSG-supported project is now starting a search for the defective WS gene by studying DNA from a relatively large number of unrelated WS patients.

Respiratory Muscle Problems in Parkinson's Disease. Research data are accumulating that indicate that in persons with Parkinson's disease the respiratory muscles appear to work against each other to create difficulties in breathing. Parkinson patients also have incomplete control of their skeletal muscles used for walking.

A BRSG-funded research fellow assisted in a Brown University (Providence, Rhode Island) study of respiratory muscle function. The muscular dysfunction became apparent when the patients attempted two tests of repetitive respiratory efforts. This was noted particularly during an inhalation test in which the participants attempted to sustain airway opening pressure while breathing through a tube that was fitted with a one-way valve and narrowed by a resistor. Eight of nine Parkinson patients could not match the respiratory work rate of the controls; their oxygen consumption for a given work rate exceeded that of normal adults during the exhausting tests.

The scientists believe that such respiratory exercises create special problems for these persons because they require repeated activation of respiratory muscle groups, turning the muscle groups on and off several times until inspiratory and expiratory muscle actions begin to overlap.

Toxic Radicals May Be Induced by Asbestos Fibers. A pilot study undertaken at the University of Texas Health Center in Tyler suggests that the presence of asbestos fibers in human lung tissue may trigger formation of free radicals, highly reactive chemical entities that cause toxic changes inside cells. The findings may help to explain the cellular mechanisms underlying asbestosis, a chronic inflammatory lung disease caused by inhalation of asbestos fibers.

Using startup funds provided by BRSG for laboratory supplies, the investigators studied the effects of amosite asbestos on cultured human endothelial cells. The investigators showed that the interaction of asbestos fibers with cells resulted in fiber ingestion by the cells as well as stimulation of the cellular metabolism of arachidonic acid, a compound that gives rise to a large number of biologically active chemicals in the body. They found that prostacyclin, the major product of this stimulation, was elevated ninefold over its levels in cells not exposed to asbestos.

More detailed biochemical studies led the investigators to propose that the asbestos-containing cells had generated a very high level of reactive oxygen radicals that injured the cells and overwhelmed their antioxidant defenses. They note that toxic oxygen radicals also have been implicated in many forms of cancer.

Scanning electron micrograph of amosite asbestos fibers that are believed to trigger formation of toxic radicals when lodged inside human cells. Fibers shown here are magnified 4,800 times.

Dr. K. S. Callahan, University of Texas Health Center at Tyler

The investigators suggest that their cell system may provide a useful model for testing other potentially hazardous chemicals and for evaluating whether or not current substitutes for asbestos may be as damaging to human cells as are asbestos fibers.

New Tools for Seeing and Measuring Brain Cell Activity. A Shared Instrumentation Grant of $114,000 to the University of Tennessee College of Medicine in Memphis has provided state-of-the-art instrumentation to help scientists at the university's Neurosciences Imaging Center learn more about several disorders of the central nervous system.

The SIG award funded the major portion of an expensive video-based image analysis system that includes a sophisticated image analyzer, a video camera, and a superb light microscope. Thus far the instrumentation has been applied chiefly to neurologic studies of motor system diseases and eye disorders.

Coupled with advances in immunocytochemistry, the video imaging system is making possible the visualization and measurement of neurotransmitters, the specialized chemicals that carry nerve signals throughout the central nervous system. Although immunocytochemistry is performed at many research centers, the research at the University of Tennessee represents one of the first times the technique has been used in tandem with video imaging to compare cells and nerve connections in healthy and diseased brains.

Some of the Memphis scientists using the system are mapping the microcircuitry of the central visual system and exploring experimentally produced alterations in neurotransmitters that may aid in understanding certain developmental disorders of the eye. Other investigators are identifying cells affected by Huntington's disease to infer the degree of cell loss at different stages of the disease. Still other Tennessee scientists have developed an approach that may pave the way to more exact measurements of neurotransmitters in specific structures of brain tissue.

A Sharper Image of Sperm Cells and Pathogens. A SIG of $400,000 to the University of Minnesota (UM) School of Medicine in Minneapolis has permitted the purchase of a Hitachi field-emission low-voltage scanning electron microscope. The instrument is illuminating many biological secrets in the life cycle of cells and disease-causing organisms, including a new look at maturing sperm cells as they traverse the epididymis.

As immature sperm begin the journey through the male genital tract, they can neither swim nor fertilize an egg. Low-voltage scanning electron micrographs obtained by the new instrument have focused on the surface of the sperm cells, monitoring the disappearance of some surface molecules and the appearance of new proteins and glycoproteins associated with motility and the ability to penetrate the zona pellucida of the egg.

Other studies under way in the university's department of cell biology and neuroanatomy are providing new information about Giardia, a diarrhea-causing protozoan that colonizes the human intestine. When fecally transmitted in its cyst stage, Giardia causes a disease that is becoming common among children in the United States under the name of "daycare disease."

Scanning electron microscopy has revealed the filamentous composition of Giardia's cyst wall and an arrangement of the filaments in circular, plaque-like configurations. Knowledge of these features may aid in designing methods to disrupt Giardia in its infectious stage and prevent its spread by fecal contamination.

Diacylglycerol in Pancreatic Cells Measured by Mass Spectrometer. Scientists at Washington University School of Medicine in St. Louis, Missouri, have used mass spectrometers purchased with a $201,000 SIG award to decipher certain complex biochemical phenomena that may be associated with the complications of diabetes.

Using mass spectrometry and enzymatic techniques the St. Louis investigators measured the biosynthesis of a substance known as diacylglycerol (DAG) that is normally present in the insulin-secreting islet cells of the healthy pancreas.

The scientists learned that high concentrations of glucose induce significant amounts of DAG that in persons whose insulin production is defective may in turn contribute to diabetes-related changes in blood vessels.

Other projects for which the newly purchased instrumentation has been employed include studies of platelet activating factor (PAF) and the proposed role of PAF in the rejection of kidney transplants.

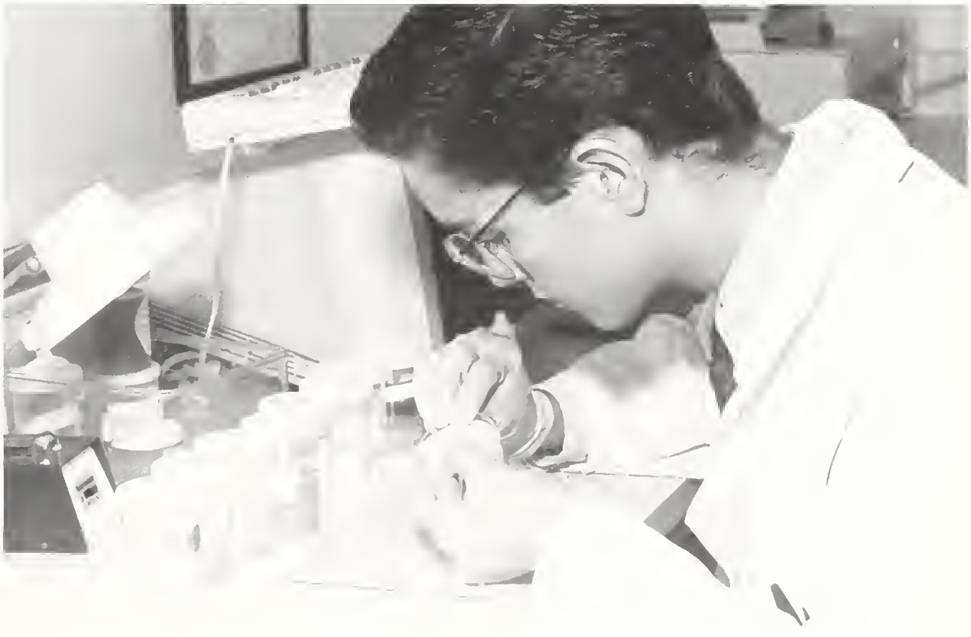
A Plethora of Genes Are Cloned on Berkeley Campus. A $300,000 SIG award to the University of California at Berkeley has equipped a new state-of-the-art microchemical facility, quadrupling the on-campus capacity for synthesizing components of DNA called oligonucleotides. The funding has facilitated the cloning of many genes, including the so-called seven-up gene, a member of the steroid receptor gene superfamily that controls the fate of photoreceptor cells during eye development.

Another gene that has been cloned in the SIG-funded facility is the mouse equivalent of a human gene that produces the CD28 antigen on the surface of immunologically important white blood cells called T cells. The CD28 antigen is thought to play a significant role in the development of T cells and in immunologic self-tolerance.

Another gene recently cloned at the facility is active during development of the central nervous system in fruit flies. It codes for a cell adhesion molecule known as fasciclin III. Research has indicated that cell surface molecules of fasciclin help to guide the developing neural pathways. Ample evidence suggests that similar neural cell adhesion molecules are active during development of the nervous system of vertebrates and fruit flies.

MHSSRA Alumni Move Ahead Into Medicine and Science. The record of success by many colleges and universities participating in the MHSSRA Program has caught the attention of scientific leaders committed to building minority representation in science and medicine in the United States. A few selected examples are:

- The Medical College of Georgia in Augusta has enrolled 26 high school students as MHSSRA apprentices since its program began in 1981. A third of the college's MHSSRA



Jorge N. Martinez, a Minority High School Student Research Apprentice, gains experience in the clinical pathology laboratory at George Washington University Hospital in Washington, D. C.

James P. Swyers

alumni were enrolled in medical school during 1990; three former apprentices have already received the M.D. degree.

- Southern University, in Shreveport, Louisiana, an institution that began its seventh year of participation in the MHSSRA Program during 1990, reported the academic success of several former MHSSRA high school students. One former MHSSRA apprentice graduated from Louisiana State University (LSU) Veterinary School in May 1990; during her sophomore year at Southern the young student had been awarded early admission to the LSU veterinary school. In the fall of 1990 another MHSSRA alumnus of Southern University gained admission to LSU Medical School-Shreveport. Yet another former MHSSRA apprentice has been admitted to a doctoral program in biochemistry at Texas A & M University.
- Another outstanding MHSSRA program is under way at Southeastern Oklahoma State University (SOSU) in Durant, an institution with a large American Indian enrollment. During 9 years of participation in MHSSRAP the university has registered 34 high school apprentices; 19 of these MHSSRA alumni have already completed their college education or are currently registered as college undergraduates. Two MHSSRA alumni are now working toward doctoral degrees in science and medicine.
- The University of Michigan College of Pharmacy in Ann Arbor has enrolled 39 high school students in its MHSSRA Program since inception. Over 90 percent of the 35 MHSSRA alumni surveyed have entered academic programs. Nine of the alumni are enrolled as engineering majors at MIT, the University of Michigan, Princeton University, Michigan State University, and Eastern Michigan University. A former MHSSRA apprentice who graduated with honors in physics from the California Institute of Technology after winning numerous national prizes in science and engineering is now a Ph.D. candidate at Harvard University. Nine former MHSSRA high school apprentices studied pharmacy, pharmacology, or biology as college undergraduates, or entered an integrated pre-medical/medical 7-year program at the University of Michigan.

Former MHSSRA Student Wins NSF Minority Graduate Fellowship. A gifted young MHSSRA alumna at the University of Hawaii at Manoa was a recent winner of the National Science Foundation (NSF) Minority Graduate Fellowship Award. Her interest in science can be traced back to when, as a high school student, she participated in the MHSSRA Program at the university's department of pathology where she learned basic laboratory skills and techniques.

In March 1990 the former MHSSRA apprentice was notified of her prestigious NSF award that includes an annual stipend for 3 years of graduate studies. In addition, NSF has awarded a $1,000 scholarship to the University of Hawaii undergraduate department of her choice as an incentive to other minority undergraduates to continue their careers in science.

The young NSF winner hopes that her graduate work at the University of California at Berkeley will lead to a career in scientific investigation.

Biological Models and Materials Research Program

Program Description

In FY 1990 the Biological Models and Materials Research Program (BMMRP) was established as a separate entity in the newly formed National Center for Research Resources. From its inception in 1985 as part of the Comparative Medicine Program, the BMMRP has provided for the development and support of nonmammalian models for biomedical research and has furnished biomaterials to the research community.

The efforts of the BMMRP are focused on increasing the variety and utility of nonmammalian models, and the program is playing an active role in developing a spectrum of model systems including invertebrates, lower vertebrates, cultured cells, and nonbiological systems such as computer simulation models. Some of these efforts may help to conserve valuable research animals as well as biomedical research funds. In FY 1990 the BMMRP funded 19 research projects and research support facilities for a total of $5.34 million.

The BMMRP supports a number of resources—facilities that supply biomaterials critical to progress in many areas of biomedical research. These resources assist individual scientists in their research by providing biomaterials and organisms; maintaining normal and abnormal cells of many species as well as viruses, bacteria, fungi, protozoa, and algae of diverse origin; establishing laboratory culture methods for nonmammalian marine organisms; and developing valuable collections of biomaterials such as cloned genes, DNA probes, and human chromosome libraries needed by the biomedical research community. The facilities include the American Type Culture Collection (ATCC) in Rockville, Maryland; the National Disease Research Interchange (NDRI) in Philadelphia, Pennsylvania; the Marine Biomedical Institute in Galveston, Texas; the *Caenorhabditis elegans* Genetics Center in Columbia, Missouri; the Yeast Genetic Stock Center (YGSC) at the University of California, Berkeley; the Repository of Human DNA Probes and Libraries located at the ATCC; and a new cell culture facility at Endotronics, Inc., in Coon Rapids, Minnesota.

In FY 1990 the BMMRP also renewed the funding of a DNA distribution facility located at the Center for the Study of Human Polymorphism (Centre d'Etude du Polymorphisme Humain), or CEPH, in Paris, France. CEPH, in collaboration with the ATCC, assembles and distributes kits of DNA probes to be used by investigators attempting to localize individual human genes. Each kit is specific to a single human chromosome and contains 5 to 15 probes. The project is part of the national effort to map the human genome.

In addition, a 1990 BMMRP grant to the Marine Biological Laboratory in Woods Hole, Massachusetts, will permit mass-rearing of the mollusc *Hermissenda crassicornis*. This marine organism will be maintained in laboratory cultures as a tool for investigating neural correlates of behavior and learning. The nudibranch mollusc may also have potential use as a new model system for studying biomineralization.

The BMMRP currently funds nine research projects to develop a variety of nonmammalian model systems. These efforts include studies on the development of isogenic strains of fish for biomedical research; use of the invertebrate animal Hydra as an in vivo cellular model in studies of basement membrane formation; establishment of a transgenic line of fish named medaka for studies of tumor development; control of morphogenesis in mollusc larvae for their use as models in studies of signal recognition/transduction; use of a computer model for predicting the behavior of the sodium/potassium pump; development of fish as a model system for bone growth and metabolism; use of the fruit fly *Drosophila* as a model system in hormonal regulation; and the examination of processing and routing events in amphibian model systems.

The BMMRP supports these diverse facilities and activities through research grants and contracts and cooperative agreements. In addition, BMMRP encourages interest in nonmammalian systems through symposia and workshops.

Consistent with the program's overall mission, BMMRP supports research on the Biomatrix, a conceptual framework for relationships among life forms that allows scientists to identify general principles pertinent to all biological systems. The Biomatrix concept is based on the idea that despite diversity of form, certain biological structures and functions are universal. BMMRP cosponsored a 3-day Biomatrix conference in July 1990 on the application to the Biomatrix of bioinformatics systems and technologies, and on the integration of organismic and molecular data bases to advance understanding and communications on the Biomatrix concept.

Program Highlights

Model Organism for the Human Genome Project. During 1990 the tiny worm *Caenorhabditis elegans* was recognized as a possible model for mapping the human genome. The BMMRP funds the *Caenorhabditis elegans* Genetics Center in Columbia, Missouri, which serves as a clearinghouse for the acquisition, storage, and development of *C. elegans* mutants.

An important addition was made to the center's collection in 1990 when two investigators at Columbia University in New York City contributed a new mutant of the nematode that appears to offer clues to Alzheimer's disease. Using an established wiring diagram of the nervous system in *C. elegans*—showing all its nerve cells and the connections among them—the Columbia University scientists identified and characterized genes that control degeneration of the nervous system. They learned that a certain gene mutation in the nematode causes an abnormal, toxic protein to be produced that causes affected nerve cells to swell and burst. The nerve cell death seen in *C. elegans* is expected to provide researchers with insights into cellular events associated with Alzheimer's disease, Huntington's chorea, and other inherited human disorders affecting the nervous system.

During the past year the center distributed 925 specimens of *C. elegans* to investigators in 38 laboratories. More than 1,200 *C. elegans* strains are available to researchers.

Improving the Tools of Neurological Research. For many years a primary tool of neurobiological research has been the giant axon, or nerve cell extension, of squid that live in the Atlantic Ocean. Scientists have tried to rear the Atlantic squid in captivity, but most of their efforts have failed. More recently, a hardy Pacific squid, *Sepioteuthis lessoniana,* has been successfully reared at the BMMRP-funded Marine Biomedical Institute (MBL) at the University of Texas in Galveston. It gives promise of becoming a more accessible biological model than its cold-water cousin.

Researchers at MBL are now trying to develop suitable conditions that will permit relatively routine culture and distribution of *S. lessoniana* and other marine organisms. Like the octopus, cuttlefish, and other cephalopods, the squid has been difficult to maintain in the laboratory partly because of its dependence upon expensive live foods, especially crabs, shrimp, and fish. The BMMRP-funded laboratory has undertaken a research program to develop pelleted diets and other types of food for cephalopods. The outcome of the effort is critical if large-scale research on cephalopods is to be conducted in neurobiology and neurochemistry laboratories located away from coastal waters.

NDRI Coordinates Pancreas Procurement for Beta-Cell Graft. Insulin-producing pancreas beta-cells transplanted to a patient with insulin-dependent diabetes mellitus temporarily eliminated the patient's requirement for insulin injections. Clinical investigators at Washington University School of Medicine in St. Louis, Missouri, performed the transplant with beta-cells isolated from cadaver pancreases provided through the BMMRP-funded National Disease Research Interchange (NDRI).

The Washington University diabetologists recently published preliminary findings on the first patient able to forego daily insulin therapy for 22 days after receiving the beta-cell transplant.

For many years squid have played an essential role in studies of nerve cell function. BMMRP-funded research at the University of Texas Medical Branch at Galveston focuses in part on developing economical ways to rear a species known as Sepioteuthis lessoniana *and to satisfy the prodigious appetites of the large numbers of squid required for neurologic research.*

University of Texas Medical Branch at Galveston

Researchers at Washington University in St. Louis prepare pancreas beta-cells for transplantation to a patient with insulin-dependent diabetes. The BMMRP-funded National Disease Research Interchange coordinated the procurement of pancreatic tissue for the study.

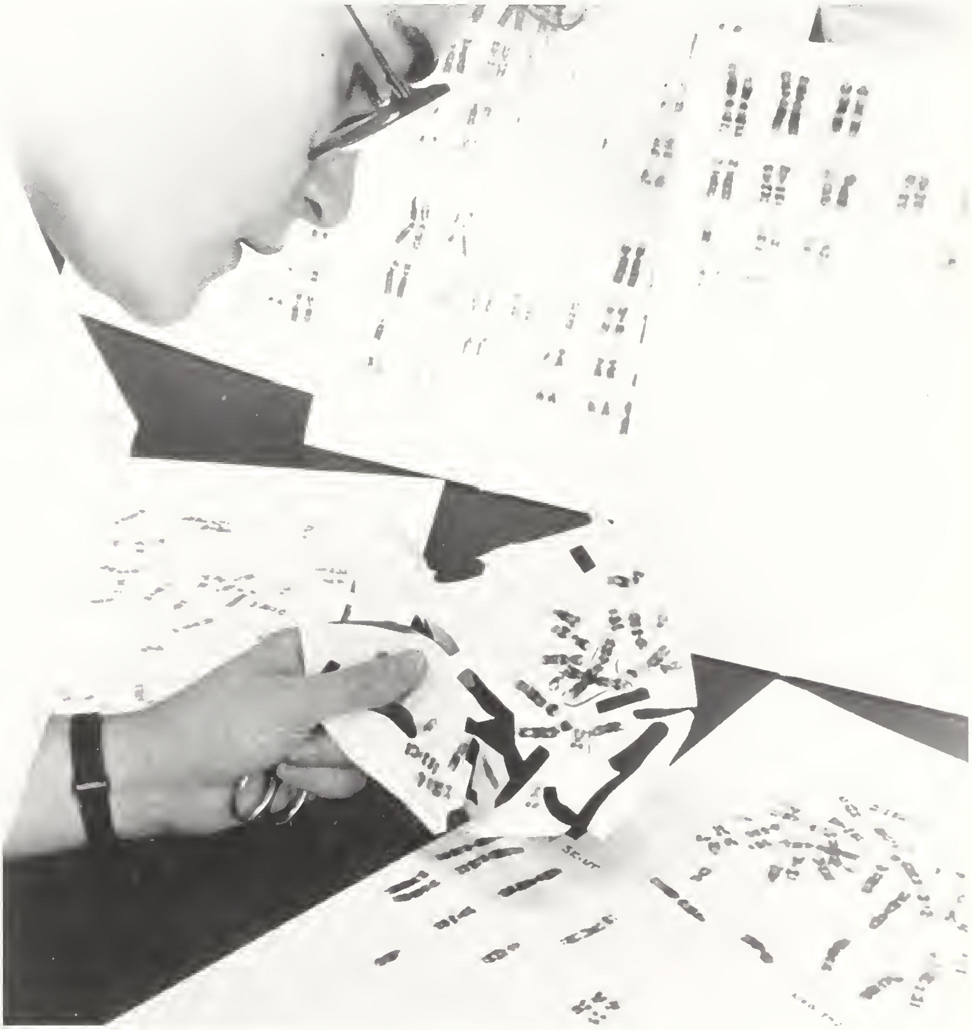
Courtesy of Washington University

The NDRI coordinates a national network for tissue and organ retrieval, processing, and delivery from its headquarters in Philadelphia, Pennsylvania. NDRI supplies organs and tissues not only to scientists studying diabetes but also to those conducting research on cardiovascular disease, cancer, cystic fibrosis, muscular dystrophy, glaucoma, retinitis pigmentosa, and more than 50 other diseases. More than 100 types of human surgical and cadaver tissue are distributed by NDRI, including specimens of the pituitary gland and the hypothalamus, eyes, liver, kidneys, and arteries. The tissues are obtained through a network of hospitals, eye banks, and organ recovery programs.

American Type Culture Collection—A World-Renowned Resource. The American Type Culture Collection in Rockville, Maryland, is a central repository for collections of a large variety of biological materials. Among them are normal and abnormal mammalian and bacterial cells, fungi, protozoa, and algae. The BMMRP-funded resource also houses extensive collections of animal, bacterial, and plant viruses and libraries of plasmids and other DNA used in studies of the structure and function of genes. ATCC supplies these important research tools to scientists worldwide. In FY 1990 more than 99,000 cultures were distributed.

The ATCC is continuously acquiring new or supplemental materials for the collections in order to maintain its position as a prime resource of biological materials. Among recent accessions were newly described strains of *Hemophilus influenzae* that cause an often fatal pediatric disease called Brazilian purpuric fever, and a very rare human medullary thyroid carcinoma cell line. After extensive experimentation, the scientists at ATCC also have succeeded in cultivating more than 100 different types of medicinal mushrooms, some of which have been used in Chinese medicine for almost 2,000 years. New therapeutic compounds may be isolated eventually from the mushrooms.

The ATCC informs the scientific community about its collections and new acquisitions in books, catalogs, newsletters, and scientific publications. In 1989 the staff wrote 44 scientific articles and distributed more than 33,000 books and catalogs.



Cytogeneticist at the American Type Culture Collection analyzes the chromosome pattern as she develops karyotypes of several human cell lines.

Courtesy of American Type Culture Collection

Research Centers in Minority Institutions Program

Program Description

Biomedical institutions known for research excellence are marked by creative environments that are linked to a quality infrastructure. Such an infrastructure requires an expert faculty with time enough for thoughtful research; modern, fully equipped laboratories and related facilities; and state-of-the-art instrumentation.

In the past institutions with large minority enrollments were often unable to offer their students and faculty members the type of research setting that is consistent with research excellence. Aware of the negative effect of this shortfall on future biomedical research in the United States, Congress in 1985 provided funds to the National Institutes of Health to establish the Research Centers in Minority Institutions (RCMI) Program. The enabling legislation focused attention on the disparity in health status between minority and white Americans and acknowledged the critical role that minority institutions have played in training the health care professionals who often serve minority populations.

The 1985 legislation provided a funding mechanism for the creation of research centers in minority institutions that award doctoral degrees in the health sciences. RCMI awards are designed to strengthen human resources and physical facilities at these institutions and to provide the equipment to conduct high quality research. New faculty members are recruited, researchers are given advanced training in new techniques, laboratories are renovated, and biomedical research capacity is enhanced by the acquisition of needed scientific tools.

RCMI support is limited to institutions whose minority enrollments exceed 50 percent. To be eligible for funding, an institution must award either an M.D., D.D.S., D.V.M., or an equivalent health professional degree; or it must have a doctoral-degree program in at least one of the health-related sciences.

Seventeen RCMI programs are in place at seven medical schools, three colleges of pharmacy, six graduate schools, and one school of veterinary medicine. The grantee institutions are in Alabama, California, the District of Columbia, Florida, Georgia, Hawaii, Louisiana, New York, Puerto Rico, Tennessee, and Texas. RCMI funding enables these institutions to improve or expand research in areas such as the neurosciences, molecular biology, immunogenetics, and other high-impact areas of investigation.

During FY 1990 funds totaling $18.9 million (including $1.27 million in National Institute of Allergy and Infectious Diseases cofunding for AIDS research and $144,000 in National Institute of Mental Health cofunding for mental health research infrastructure) were awarded to advance the RCMI programs at the 17 institutions, including seven awards to institutions that competed successfully for renewal of their RCMI programs. For example, the Meharry Medical College in Nashville, Tennessee, received an RCMI renewal grant for a 5-year period. RCMI funding was designated for three areas in particular: infrastructure, the neurosciences, and research on acquired immunodeficiency syndrome. Infrastructure funds were earmarked for research support services at Meharry, facilities for the optimal care of laboratory animals, and improvements in the areas of computer science and electron microscopy. Neuroscience funds covered recruitment of faculty members with expertise in biochemical and molecular neuroscience. AIDS-related funds were designated to hire faculty skilled in immunology, virology, epidemiology, and behavioral research to undertake a pilot study on the immune system of newborn infants at high risk of developing AIDS.

Hunter College of the City University of New York was awarded a 5-year renewal grant effective October 1, 1990, to strengthen infrastructure at its Center for the Study of Gene Structure and Function and for studies of AIDS and AIDS-related complex (ARC).

The Ponce School of Medicine in Ponce, Puerto Rico, also received a 5-year renewal award effective October 1, 1990, to launch an ambitious, multifaceted effort. The grant is enhancing the institution's infrastructure by funding a series of visiting consultantships, upgrading library and animal care facilities, and supporting a variety of research investigations. Included will be research in clinical immunology and immunochemistry, environmental toxicology, cardiology, cerebral injury in the perinatal period, and pediatric

At the Ponce School of Medicine in Puerto Rico pediatric pneumonologist Dr. Felix Cohen and pharmacologist Dr. Teresa Frazer monitor glucose levels in an infant with cerebral injury.

Ponce School of Medicine

AIDS—particularly an assessment of the AIDS epidemic in southern Puerto Rico, including the transmission of HIV to nursing infants.

During 1990 RCMI program directors organized and sponsored a significant series of scientific symposia at RCMI institutions concerning two major areas of contemporary bioscience: AIDS research and mapping the human genome. The Hunter College symposium focused on developing antiviral drugs effective against AIDS. At the University of Puerto Rico's Medical Sciences Campus in San Juan, the symposium's emphasis was on AIDS among ethnic and racial minorities and pediatric AIDS; the sessions were designed for physicians who treat AIDS patients and for basic and clinical scientists pursuing AIDS research. At Morehouse School of Medicine in Atlanta, Georgia, an international symposium examined the impact of AIDS on populations in Africa and Latin America and on minority populations in the United States. AIDS epidemiology, vaccine development, education, and prevention and treatment strategies were discussed.

RCMI investigators involved in projects related to the Human Genome Initiative presented their studies at a meeting in Nashville, Tennessee. They are described under *Research Highlights.*

Research Highlights

Plotting Strategies in the Human Genome Initiative. Advances in the sophisticated technology of DNA sequencing made at Meharry Medical College during the year were reported at a preliminary planning meeting on the Human Genome Initiative. An RCMI-funded Meharry scientist described an improved method for determining the sequence of nucleotides—the building blocks—in DNA. The new approach will overcome shortcomings in conventional procedures by allowing internal regions of cloned DNA to be directly accessible for sequencing in one step. More information will therefore be obtained in a shorter time than previously. In principle, the molecular biologist from Nashville reported, the improved method could be useful in experiments with any recombinant DNA.

At the same meeting, which was cosponsored by the National Center for Human Genome Research and the RCMI Program, an immunogeneticist supported by the RCMI at Howard University in Washington, D.C., described her studies of a series of genes on chromosome 6 that control immune defenses of the cell-mediated type. The genes code for the human leukocyte antigens (HLA) that are present on the surface of white blood cells. Both whites and blacks have a large variety of different HLA types, but the Howard investigator has found a greater HLA diversity among African-Americans than among Caucasians. In studying HLA diversity in patients with insulin-dependent diabetes mellitus (IDDM) she and her colleagues found a certain HLA type to be associated with IDDM susceptibility; a genetic determinant unique to and common among African-Americans was associated with resistance to IDDM. The RCMI-supported geneticist also has reported an association of another HLA type with susceptibility to vitiligo, a skin disease believed to be of autoimmune origin.

Other RCMI-funded scientists reported research findings that may contribute valuable information to the human genome project. In studies of the fruit fly genome at the University of Hawaii in Manoa the mapping of the tightly coiled DNA-protein complex called heterochromatin has been explored during the past year. An RCMI-supported scientist at Manoa reported data on the structure of the heterochromatin that are expected to be useful in mapping the human genome.

Signal transduction, the transmission of signals from receptors on a cell membrane to genes inside the cell nucleus, has been explored intensively at the RCMI-supported Center for the Study of Gene Structure and Function at Hunter College of the City University of New York. The Hunter College scientist described his use of the slime mold *Dictyostelium* in studies that showed that extracellular cyclic AMP behaves as a hormone by binding to cell surface receptors and inducing several genes. He found that the final step in the pathway, gene induction, involves binding of cellular nuclear proteins to a particular site on the affected gene. Research on this mold, which is a relatively simple genetic entity, is expected to facilitate similar efforts in the more complex human genome.

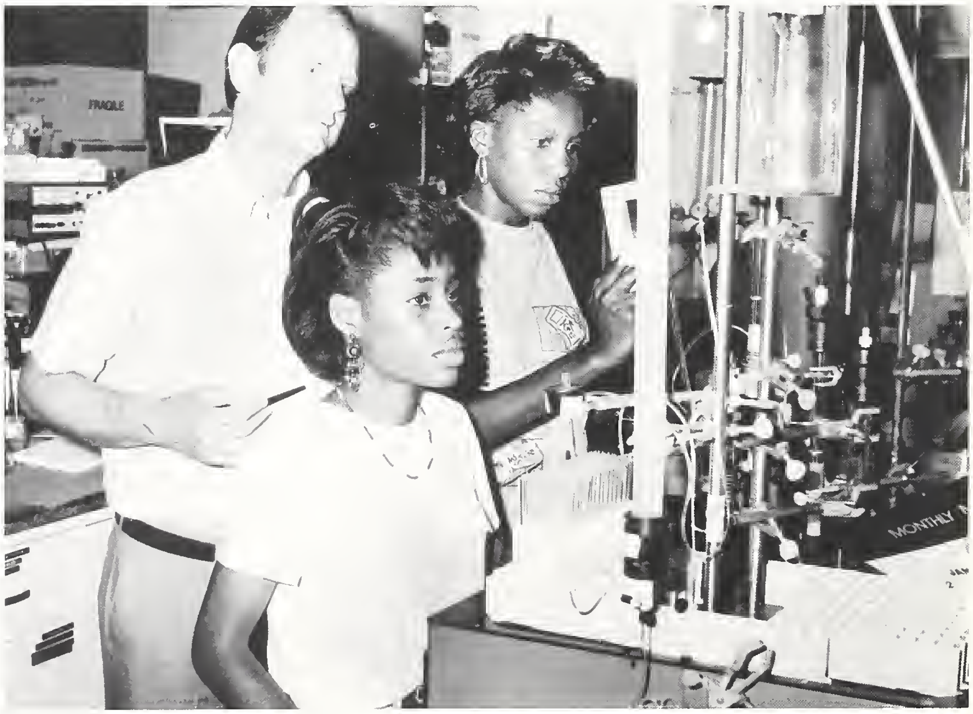
Therapeutic Advances in Fabry's Disease. RCMI-funded scientists at the City College of New York (CCNY) made progress during 1990 toward developing a treatment for the rare inherited disorder called Fabry's disease. Fatal in early or middle adult years, Fabry's disease is an inborn error of metabolism characterized by a deficiency of the enzyme alpha-galactosidase A. The enzyme deficiency makes it impossible for the body to metabolize many carbohydrates and lipids, which therefore accumulate in the tissues. Patients with Fabry's disease experience excruciating pain.

Until now, enzyme replacement therapy was not a promising approach; inadequate supply of the missing enzyme was a limiting factor. However, after an RCMI-funded scientist isolated the human gene coding for alpha-galactosidase A, recombinant DNA technology has made the enzyme available in virtually unlimited quantities. Alpha-galactosidase A produced by recombinant DNA technology appears to be incorporated efficiently into cultured cells from patients with Fabry's disease. The investigators hope that clinical trials may soon be possible.

Evaluating Cardiovascular Effects of Caffeine and Mental Stress in Blacks and Whites. Different results were observed for men and women when investigators at the Charles R. Drew University of Medicine and Science in Los Angeles, California, studied the combined impact on blood pressure of caffeine and a mental arithmetic stress test in healthy young black and white men and women.

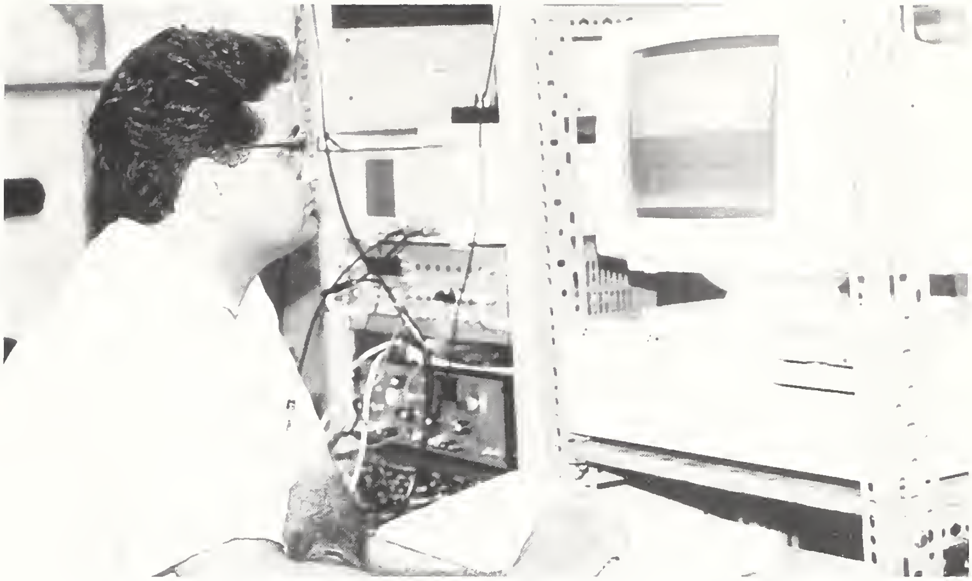
In the first study 40 black and white men who were regular coffee drinkers were studied; 20 of them—10 of each race—had a family history of hypertension but all had normal blood pressure. The men received two doses of caffeine or placebo, administered in decaffeinated coffee in a double-blind type of study. Blood pressure and heart rate were subsequently measured, and the arithmetic stress test was administered.

After caffeine administration the men had higher blood pressure than after placebo



Research in enzyme replacement therapy for Fabry's disease is being sponsored by the RCMI Program at City College of New York (CCNY). In the effort to develop effective treatment for this inherited disorder, Dr. David Calhoun and students Ihuoma Alozie (left) and Janice Riley employ sophisticated techniques of recombinant DNA technology.

P. J. Carvalho



Neurophysiologist Dr. Sukhbir S. Mokha at Meharry Medical College in Nashville, Tennessee, studies compounds that block kappa opioid receptors in the medullary dorsal horn of the rat brain, inhibiting transmission of painful sensations from the facial area.

Courtesy of Meharry Medical College

administration, but contrary to expectations, racial and family history differences did not affect the results. Mental stress and caffeine had an additive effect on blood pressure. Young black men with a family history of hypertension, however, were slower to recover their normal blood pressure than were white men with a similar family background. Heart rates were higher overall among whites than blacks, but this difference was unrelated to caffeine or the mental stress test.

When comparable testing was conducted among 48 normotensive black and white women who were not regular coffee drinkers, caffeine increased the blood pressure only during periods of mental stress. As with men, caffeine had little effect on heart rate, and the effect on blood pressure was unrelated to race or a family history of high blood pressure.

The investigators suggest that the patterns of hemodynamic response to caffeine and psychological stress in men and women merit further examination. The studies are part of a larger program at the Drew University RCMI to investigate why blacks are at a disproportionately higher risk of hypertension and its consequences than are whites and other population groups.

Pain Receptors Studied in Cells of the Spinal Cord. During the past year neurophysiologic studies were conducted at Meharry Medical College of the transmission of painful sensations received by nerve cell receptors in an area of the spinal cord called the medullary dorsal horn. This is a nerve center that influences sensory information affecting the face.

The neurophysiologists conducted their research with anesthetized rats that were given various compounds that blocked or, in some cases, heightened the sensation of pain caused by extreme heat. Dynorphin, a naturally occurring opioid compound, reduced the input of painful signals caused by a heat stimulus at some of the receptors in the dorsal horn; in other cases it increased the thermal effect, and in still others it had a biphasic effect.

An experimental synthetic opioid compound, code named U-50,488H by the manufacturer, reduced pain sensations in the superficial layers of the dorsal horn; however, deeper in the dorsal horn the responses of multireceptive nerve cells were variously reduced or enhanced.

Evidence of the activity of these compounds in affecting the sensation of pain was determined by measuring evoked responses through extracellular single unit recordings. The Meharry RCMI scientists are continuing their studies of multireceptive nerve cells in the dorsal horn and ways in which pharmacologic agents affect the sensation of pain.

Intramural Programs

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Overview of Intramural Research Resources Actual Obligations

National Center for Research Resources Overview of Intramural Research Resources FY 1990 Actual Obligations

Program	Management Fund*	Service And Supply Fund	Total
Office of the Director/ Office of Animal Care and Use	$ 4,594,000	$ 524,000	$ 5,118,000
Biomedical Engineering and Instrumentation Program	$ 3,172,000	$ 8,763,000	$11,935,000
Library Branch	$ 4,332,000		$ 4,332,000
Medical Arts and Photography Branch		$10,311,000	$10,311,000
Veterinary Resources Program	$ 5,829,000	$11,474,000	$17,303,000
Total	$17,927,000	$31,072,000	$48,999,000

* Does not include reimbursements or charges related to space costs.

Biomedical Engineering and Instrumentation Program

Program Description

The Biomedical Engineering and Instrumentation Program (BEIP) is a centralized resource at the NIH, contributing to advances in biomedical research through applications of engineering, mathematics, and the physical sciences. BEIP's staff of approximately 40 physical scientists and engineers and 75 technical support personnel collaborates each year on more than 200 projects to produce advanced instrumentation, models, and techniques dedicated to the acquisition of biomedical information previously unavailable to NIH scientists. In addition, they typically respond to about 1,400 requests for fabrication or major modification of laboratory devices and nearly 10,000 requests for repairs and minor modifications of scientific equipment.

BEIP is composed of two parts—Professional Engineering and Scientific Equipment Services.

Professional Engineering. BEIP's engineers and physical scientists collaborate with intramural NIH scientists—and do independent research—on biomedical measurement, mathematical modeling, imaging, and the design of specialized instrumentation. These staff members work within sections devoted to applied clinical engineering, chemical engineering, electrical and electronic engineering, and mechanical engineering, and in specialty groups engaged in pioneering research in magnetic resonance imaging, digital image processing, analytical electron microscopy, and ultracentrifugation. BEIP also has administrative responsibility for and provides major technical support to the NIH In Vivo NMR Research Center.

Scientific Equipment Services. The staff of instrument makers and medical and scientific equipment specialists provides technical services in support of the intramural research program, including construction, modification, repair, sale, and lease of scientific equipment. Capabilities include the ability to make sophisticated instruments that comprise electronic components, large or miniature mechanical components, polymers, and glass. BEIP offers NIH researchers a variety of comprehensive plans for maintenance and repair of scientific equipment, clinical equipment, and personal computers. BEIP's Scientific Equipment Resources Program sells and leases commonly sought scientific equipment, offering researchers shortened procurement times, flexibility in configuring their laboratories, and cost savings.

Research Highlights

Aging

Monitoring Wandering Alzheimer Patients. Patients with Alzheimer's disease and other types of dementia can be difficult to manage on a ward or in other clinical settings because they tend to wander. BEIP engineers have been working with NIH Clinical Center staff to develop an electronic system capable of monitoring the location of wandering patients and controlling their exit from the ward without resorting to confinement. The system uses a very low-powered radio transmitter worn by each patient that transmits with a unique modulation frequency to permit patient identification. The radios resemble a wrist watch—a regular hospital identification bracelet serves as the watch band—and are engineered to enhance battery life.

Antennae located near each door of the ward pick up signals transmitted by the radios regardless of the patient's location. A microprocessor-based control unit receives the signals and processes them. If required, the unit can produce audio alarms and generate lock control signals that are interfaced with the building fire alarm system. Data on each patient are also transmitted to a personal computer at the nurse's station.

Similar systems are being developed for other NIH wards with similar problems, and the technology has been shared with a national inter-agency group.

Microdialysis Probes. Parkinson's disease is characterized by changes in the level of dopamine, a biochemical messenger found in the brain, but exactly how this causes the symptoms and signs of the disease is unclear. BEIP engineers have developed a microdialysis probe that is capable of sampling the concentration of dopamine and biochemical products related to its breakdown in the brain as part of a study of Parkinson's disease. The microdialysis probe is a small, cylindrical tube about the size of a hypodermic needle surrounded by a thin, semipermeable membrane that allows the passage of certain molecules. The inside of the tube contains a solution that collects the molecules. When the probe is withdrawn, the concentration of the molecules within the solution can be correlated to the original concentration within the brain, using complex mathematical models developed by the engineers.

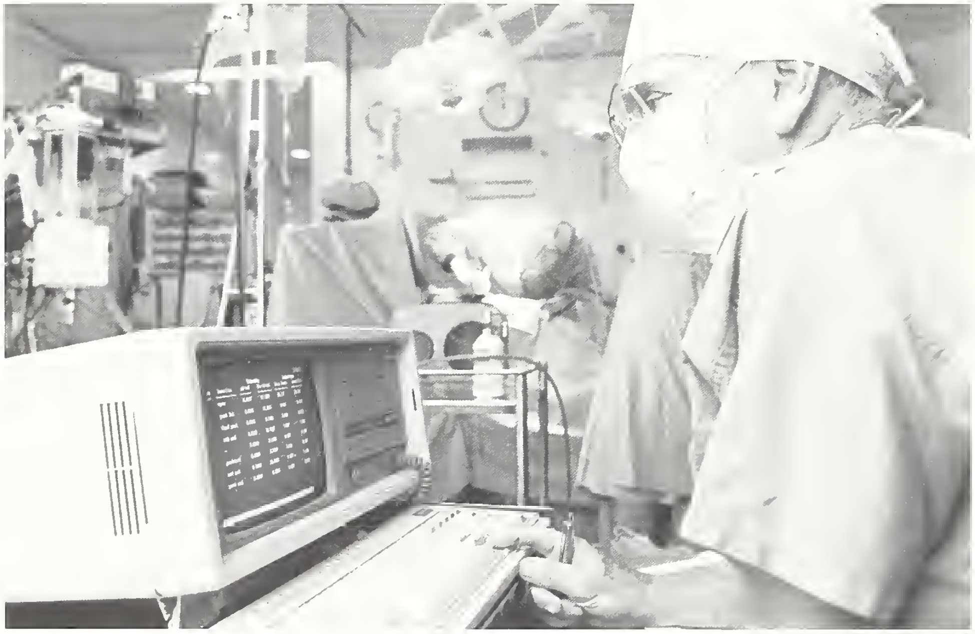
In addition to sampling areas such as the brain, the probe can also be used to infuse drugs in solution into very specific areas of the body.

Cancer Treatment

Photodynamic Therapy. A new therapy for many different types of cancer has been developed by BEIP engineers in collaboration with physicians and researchers in the Surgery and Radiation Oncology Branches of the National Cancer Institute. Called photodynamic therapy, the treatment initially involves administration of a light-sensitizing drug to the patient that concentrates in malignant tissue. About 2 days later intense light is delivered by laser to the cancer site. The light activates the drug and causes it to convert oxygen to a highly toxic state called the singlet state, which kills cancer cells in the area.

The types of cancer treated so far with photodynamic therapy include bladder, skin, and bronchial cancers, among others. BEIP personnel have developed the laser light delivery system as well as instrumentation to monitor light delivery during treatment. The therapy and instrumentation are constantly being updated, so engineers continue to be prominently involved in many operations.

Investigations are continuing into understanding how the light behaves in tissues of the body, which wavelengths of light are the best to use, and what depth of treatment produces the best results.



Walter S. Friauf, Chief of the Electrical and Electronic Engineering Section, BEIP, monitors the light dosage during photodynamic therapy for cancer. The equipment was designed and manufactured by BEIP personnel.

John Crawford, NCRR

Hyperthermia. Heat therapy, or hyperthermia, can be effective in treating cancer if the temperature in the tumor is raised to between 42 and 45 degrees Celsius (approximately 107 to 112 degrees Fahrenheit). Results from treating deep tumors, however, have not been as good as those from treatment of superficial tumors because the ability to measure temperatures in a deep tumor has been limited.

Engineers at BEIP are working to develop a technique that will enable them to measure temperature in a tumor very precisely. They are using a type of magnetic resonance imaging called intravoxel incoherent motion, or IVIM. IVIM relies on mapping the difference in two images of the tumor site: one made before heating and one during heating.

In laboratory tests of IVIM the technique was found to measure temperature changes with a high sensitivity. A clinical study using IVIM imaging together with a heat delivery system, also developed by BEIP engineers, will soon be under way.

Dr. Robert Lutz of the Chemical Engineering Section, BEIP, and registered nurse Judith L. Collins are working with a mechanical vascular system model designed by BEIP engineers. The blood flow in arteries, veins, and the heart can be assessed with this model.

Bill Branson, NCRR

Immunotoxins. Finding a way to specifically target cancer cells for destruction while leaving the healthy cells intact has long been a goal of cancer treatment specialists. With the help of BEIP engineers progress is being made toward the development of more specific drugs.

Engineers in the Chemical Engineering Section have been studying the properties of immunotoxins—biological toxic compounds linked to antibodies specific for tumor cells—in animal models of human cancers. The antibody portion of such "magic bullets" will specifically seek out cancer cells and the toxin component will interrupt growth of these cells. The naturally occurring diphtheria toxin has been under study for use in these compounds.

Engineers are studying how diphtheria toxin alone and in combination with the antibody is dispersed in various tissues, both in mathematical and animal models. Animal models are also being used to examine the distribution of the immunotoxin over time to determine how specifically and rapidly the toxin disperses.

These experiments will provide the data clinicians will use eventually to determine the proper dose and regimen for treating humans with immunotoxins.

Cardiovascular Studies

Cardiovascular Dynamics. Engineers in the Theoretical Biomechanics Group of the Mechanical Engineering Section are developing theoretical models in the area of cardiovascular dynamics, which describes how the heart performs its work. When their models are used in conjunction with clinical data and data obtained from laboratory animals, a clearer understanding of heart function in normal and diseased states emerges.

The engineers' model data are being used in several projects. Among them is a collaboration with French scientists in the use of echocardiography to examine and evaluate without invasive techniques the severity of congenital heart disease in infants. In collaboration with the Cardiology Branch of the National Heart, Lung, and Blood Institute a study is under way to noninvasively assess the inherent strength of heart contraction in a population of normal patients. Another study has validated a model for blood flow in the heart and is being used to examine alterations in blood flow during a variety of disease states.

A model that is currently being designed may provide information about the decreased pumping capacity of the heart following a heart attack.

Hemodynamics. How blood flows in veins, arteries, and the heart can be conveniently assessed with a mechanical flow model of a vascular system developed by BEIP engineers. Such information is extremely useful to clinicians. For example, models of the human carotid and hepatic artery systems have been used to study the degree of mixing that occurs between blood and solutions infused into the arteries via intra-arterial catheters. These models have aided in the development of improved catheters that promote more even distribution of drugs into target tissues.

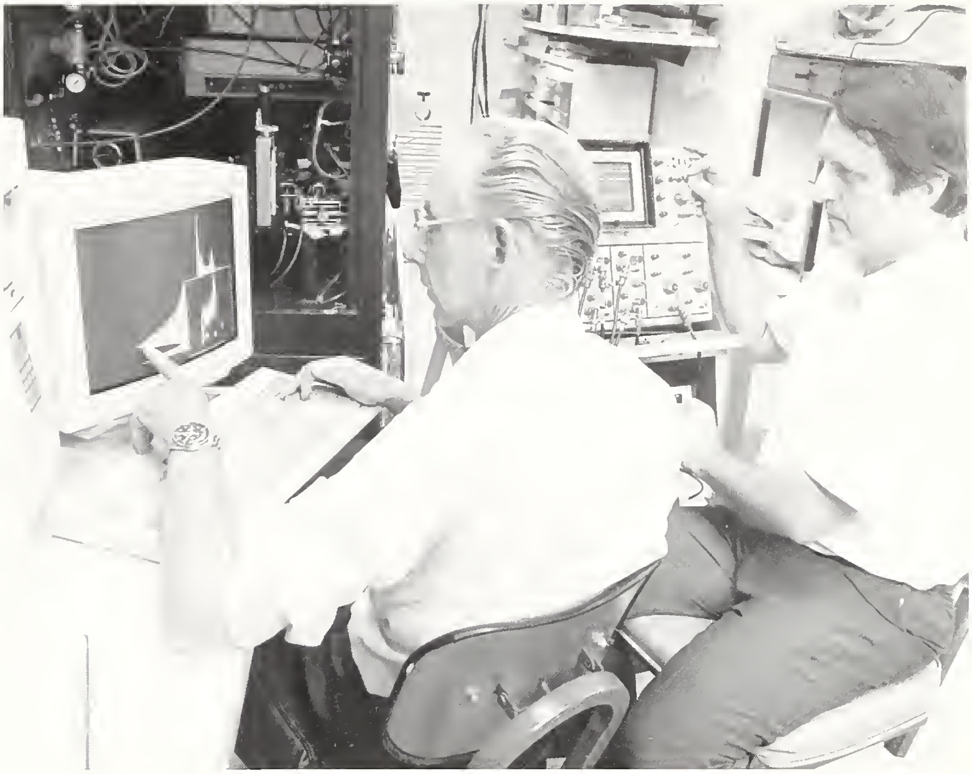
A model of the vena cava was used to study the effects of simultaneous infusion of incompatible drugs through a multilumen catheter. A precipitate of the two drugs formed at the mixing site.

Models of human coronary arteries are helping engineers to understand the conditions that produce turbulent flow in these vessels and to visualize the changes in flow that accompany insertion of an intravascular support device called a stent. Stents are commonly placed in weakened arteries following angioplasty and the studies may provide clues to the causes of stent failure as well as suggest ways to improve stent design.

Special Instrumentation

Flow Cytometer Interfacing. Flow cytometers, instruments capable of producing data about particles that flow past a beam of light or electronic circuitry, are increasingly used in clinical settings, particularly to produce information about cells. However, errors can arise when a computer records the data due to lack of synchronization between the computer and the cytometer's interface—the technology by which the device and computer communicate.

Engineers at BEIP have developed a relatively inexpensive electronic interface for use with an inexpensive microcomputer. During the development stage of the interface, several problems inherent in commercially designed flow cytometers were identified and corrected. In addition, user controls were arranged so they may be operated in an "intuitive" manner and in the low light conditions that are common when using flow cytometers. A simple oscilloscope is required to monitor the system, align the optics, and set up the interface.



Courtney Mudd (right) of the Applied Clinical Engineering Section discusses a flow cytometry experiment with Dr. James Dvorak of the National Institute of Allergy and Infectious Diseases. BEIP engineers have developed a novel electronic interphase between the flow cytometer and its associated computer.

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The advantages of the interface include its low fabrication cost, its capacity to be integrated into existing systems, improved performance and resolution, and operational simplicity. A flow cytometer using the interface has become an integral part of research on the molecular basis of infectious diseases by the National Institute of Allergy and Infectious Diseases.

Confocal Microscope. Confocal microscopes are capable of producing better images of specimens under study than conventional microscopes because they eliminate out-of-focus light. They do this because a pinhole in the optical path produces an optical sectioning effect and allows three-dimensional images to be reconstructed. This enables depth as well as magnification information to be obtained.

Engineers at BEIP have developed a confocal microscope that is capable of producing real-time images. As with other video microscopes, this confocal microscope provides the opportunity for computer manipulation of images as well. Engineers believe this microscope will be useful for studying dynamic images such as live cells.

Sleep Study Instrumentation. A thorough understanding of the psychobiological mechanisms involved in sleep is necessary to understand the effects of sleep deprivation and disturbance. BEIP engineers have been working in collaboration with the Clinical Psychobiology Branch of the National Institute of Mental Health to develop a computer-based system for investigating sleep disorders. Rats, which have sleep behavior similar to that of humans, are being used in the investigations.

Current sleep studies involve the simultaneous measurement of a combination of physical parameters, including heart rate, core temperature, and brain temperature. Electrical measurements of the brain (EEG) and muscle (EMG) are also taken.

Data are fed into a microcomputer-based system that accepts, analyzes, and stores the data. The system can accept fast as well as slow data simultaneously and is capable of handling data from three stations.

Scratching Assessment. Patients with primary biliary cirrhosis, a liver disease, suffer from severe bouts of itching, which is manifested clinically by chronic scratching. In order to evaluate the efficacy of experimental drugs that may relieve the itching, BEIP engineers have developed a system to measure scratching.

The system uses a transducer cemented to the patient's primary scratching fingernail, which transduces the mechanical vibrations generated by scratching to a miniature FM transmitter. The signals are then transmitted to an FM receiver and from there to a frequency counter and personal computer.

The scratching assessment system has been used successfully to evaluate one anti-scratching drug, and additional studies are under way.

Library Branch

Program Description

The NIH Library is an open-stack biomedical research library, open 365 days a year, with collections and services developed to support NIH programs. An annex to the library, located a few miles away, was originally designed for storage only but now also offers reference and computer search services for local NIH staff. The public may use the NIH Library for reference purposes only. The library has closed carrels for its clientele that allow space and privacy for preparation of speeches, papers, or other work that may require library research. Use of the library has increased in the past 3 to 10 years, as demonstrated by the number of persons entering the library, the number of photocopy requests, and the number of items shelved.

Each month more than 30,000 people enter the library, and 3,000 to 5,000 books are circulated. The journal collection does not circulate unless there are two copies of a particular title. An integrated computer system controls acquisitions, catalog, serials, and circulation functions. Journal holdings appear in the catalog, with the daily journal receipts visible.

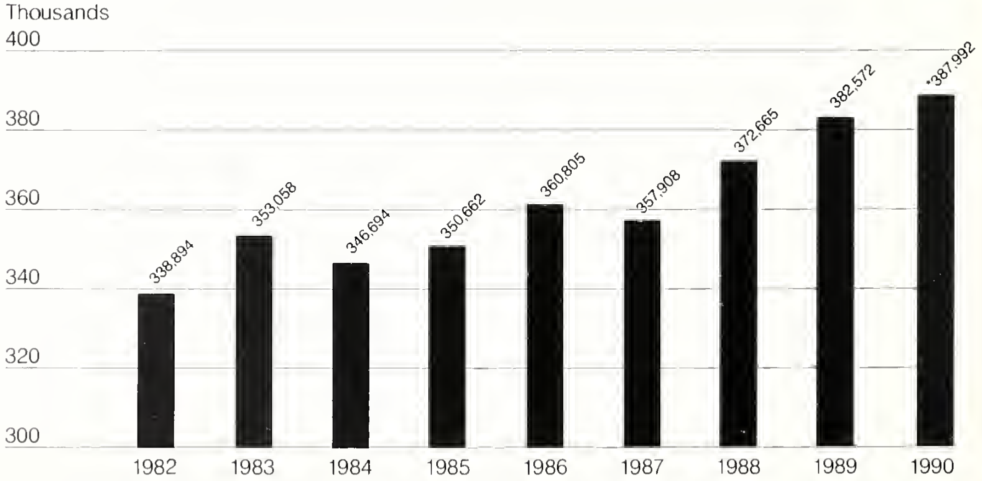
With a collection of approximately 85,000 monographs, 160,000 bound periodicals, and 3,500 current journal titles, the NIH Library is among the largest biomedical libraries in the country. The majority of the collection is in biomedical research fields including physiology, biology, chemistry, and physics. Small collections are also maintained in areas of interest to administrative personnel.

Books are reshelved continuously during working hours, resulting in approximately 650,000 books being reshelved in a year. The standard for reshelving requires that 85 percent of material should be shelved within 4 hours and 99 percent within 6 hours of receipt.

The 55-person library staff, which is supplemented by contract staff for support functions, offers a range of services—among them, translation of foreign languages, clinical library service, computer software applications, and photocopying—that has been increasing in both volume and variety. The library's translation unit is staffed by two translators. About 20 percent of the translations are prepared on contract. The library has a staff clinical librarian who attends medical rounds and has special programs for AIDS, cancer, heart disease, and dental disease clinics.

Librarians expert in library software applications offer advice and assistance in using software to control small collections or create bibliographies. The library's staff also offers

National Institutes of Health Library
Gate Count (Number of Persons Entering the Library)
September 1990



*Total based on 11 months data for FY 1990 and projection for September

The NIH Library has a collection of approximately 240,000 volumes and 3,500 current subscriptions. More than 1,000 persons visit the library each day.

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tutorials and classes in basic searching techniques using standard MEDLINE and GRATEFUL MED, a program designed by the National Library of Medicine. The library has access to more than 400 computer data bases, including those on the systems DIALOG, MEDLARS, BRS, STN, and Mead Data Central. The library staff performs approximately 1,100 computer searches each month. Selective dissemination of information services is also available to NIH staff. Approximately 450 searches are stored on SDILINE, TOXLINE, AIDSLINE, and CANCERLINE, with monthly bibliographies distributed.

Photocopying is another service provided by the library staff. Approximately 4.25 million photocopies are made each year by NIH staff for their own use and by library staff for their clientele. Ninety-seven percent of document requests, including requests for photocopies, are filled. The majority, 83 percent, of document requests are filled from the library's own collection and 14 percent from other libraries such as the nearby National Library of Medicine.

The Library will be facing increasing operating costs in the upcoming fiscal year, especially for book and journal acquisitions. Journal subscription prices increased tremendously in the early eighties, then steadied somewhat. Prices for 1991 are again climbing, with predicted increases of 9 to 12 percent in domestic and up to 37 percent in foreign publications. Book prices are equivalently affected.

Because of these rising costs the library staff must carefully evaluate the usefulness of each journal subscription. A total of 180 titles have been removed from the renewal plan for 1991, and the staff will continue to study each journal's use in relation to its cost so that the most useful collection can be maintained.

Medical Arts and Photography Branch

Program Description

The Medical Arts and Photography Branch (MAPB) is a central service organization that provides a wide variety of visual communication services to the NIH community. MAPB's products and services visually document scientific data, research programs, events and accomplishments for use in publications, exhibits and presentations to the worldwide scientific community and the general public. Over 75,000 requests for services are expected to be completed this year, with the total output for pieces of work to exceed 1.5 million.

Professional artists and photographers make up the MAPB staff, combining their visual expertise with the needs of scientists for graphic presentations, medical arts, photography, and video productions. Services include design and production of publications, preparation of slides, viewgraphs and other projected visual aids, exhibit design, statistical drafting, display charts, posters, medical illustrations, video recording, and support for special events.

MAPB's long-standing philosophy is to provide high quality professional services competitive in cost with commercially obtainable services. Competition among qualified vendors and daily bid sessions are conducted to ensure cost effectiveness while maintaining quality.

MAPB continues to update equipment in order to meet the ever-changing demands for services. The purchase of Macintosh II computers enables skilled MAPB staff members to offer computer-enhanced publication designs to their clients.

A productivity study currently under way will be completed in March 1991. This study is being conducted to help MAPB management strengthen program objectives, assess performance indicators, and identify major problems and issues.

MAPB is divided into sections, which include photography, design, graphics, and medical illustration. The Photography Section provides central photographic services to the NIH community, including information, patient and surgical photography, micro- and macrophotography and photographic laboratory processing. A diverse range of photographic facilities are used to accommodate the high volume of requests received each day. The Photography Section is currently evaluating the demand for digital enhanced electronic imaging for photomicrography within the NIH community.

The Design Section provides publication design for public information, scientific presentations, conferences, posters, editorial and technical illustrations and provides other services required to support NIH research. Many of the section's graphic designers and illustrators have won awards for their designs in local, national, and international competitions, including a silver medal for a poster designed for an NIH campaign that encouraged employee vaccination against measles.

Linda Brown (left), Chief of the Design Section of the Medical Arts and Photography Branch, looks at possible color combinations with Richard Barnes and Margaret Georgiann, whose measles vaccination poster was awarded a silver medal for design excellence by the Art Directors Club of Metropolitan Washington.

Bill Branson, NCRR

The Graphics Section employs illustrators, visual information specialists, exhibit specialists, and TV production specialists and provides illustrations, graphs, charts, tables, slides, computer-generated graphics and other materials for scientific presentations and publications. The Special Events Unit within the section provides support for one-time or unusual events, as well as videotaping services. The newly renovated edit suite now enables the Special Events Unit to offer in-house videotape editing. Many public service announcements developed for various NIH institutes are coordinated and produced in-house. Recently a public service announcement entitled "Stop Smoking" won second place in an international television video competition.

A wide variety of black-and-white and color medical illustrations are produced by the Medical Illustration Section. Diagrams of surgical gross pathological, biological, and dental subjects are also produced. In addition, the Medical Illustration Section provides illustrations to be used by other sections in poster designs, publications, exhibits, and newsletters. The section is currently involved in a long-term illustration project entitled "Atlas on Oncologic Surgical Techniques."

Veterinary Resources Program

Program Description

The Veterinary Resources Program (VRP) provides comprehensive professional and technical support for biomedical research at the NIH. The program was reorganized in 1990 to more clearly delineate its functional responsibilities and to recognize its research role in the field of laboratory animal science. The program is now divided into two branches, each comprising three sections.

The Research Animal Branch comprises the Carnivore and Ungulate Section; the Primate Section; and the Rodent and Rabbit Section. The Scientific Services Branch comprises the Genetic Resource; Laboratory Sciences; and Surgery, Radiology, and Pharmacy Sections.

The program obtains, houses, manages, and offers professional and technical services in support of research colonies of nonhuman primates, dogs, cats, rodents, rabbits, and livestock used by the intramural programs of NIH institutes, centers, and divisions as well as by those of the ADAMHA, FDA, and other Federal agencies.

Central animal surgery and radiology facilities are also managed and operated by VRP to aid investigators whose work requires these specialties. To ensure that the health of research animals is properly maintained, VRP has an animal health surveillance program that provides expertise to perform special diagnostics and disease control. In further support of biomedical research, VRP provides consultative services to NIH scientists and others throughout the world on animal health, care, husbandry, genetics, and nutrition.

The VRP manages the NIH Animal Genetic Resource (NIHAGR), which contains more than 300 rodent and rabbit strains, congenics, recombinant inbreds, stocks, and mutants that are maintained or being developed as models of human disease. Breeding nuclei from this resource are provided to public and private institutions around the globe. The NIHAGR is designated by the World Health Organization as a Collaborating Centre for Defined Laboratory Animals and by the International Council for Laboratory Animal Science as a Nude Mouse Repository.

In FY 1990 short- and long-term plans to renovate existing facilities and provide new facilities to house and use research swine, dogs, rodents, and rabbits were developed and implemented. In existing buildings the goal is to optimize the quality of animal space and maximize its usefulness to NIH intramural scientists. VRP plans and provides management and operational support in several new central animal facilities. For example, significant progress was made toward opening a centralized rodent and rabbit building early in FY 1991. In addition, the design phase was initiated for new facilities for small ungulates and transgenic rodents and for renovation of existing primate and dog facilities.

Research Highlights

NIH Animal Genetic Resource (NIHAGR)

Special Strain Development. Animals with certain genetic deficiencies are useful models for studying similar human diseases. The NIHAGR has become a center for development of immunodeficient mice and rats that may provide information about diseases and techniques in humans that include cancer, transplantation of organs, and the ability of the body to fight infections of bacteria and viruses. In mice the developmental programs have centered on three types of immune deficiencies, each the result of a mutation. These are known as the beige *(bg)*, nude *(nu)*, and x-linked immune defects *(xid)*. So far, there are 30 strains of mice with the *nu* gene, 16 with the *bg* gene, and 25 with the *xid* gene. Mice bred to have all three mutations may be a model in which the function of human lymphocytes can be studied. Scientists have shown that these important immune cells can survive in the spleens of these mutant animals.

The nude mutation has been established on 13 different rat strains. Combinations of the nude mutation with mutations that cause jaundice and diabetes insipidus have also been developed. In addition, rats homozygous for the osteopetrosis gene are available. These rats not only demonstrate problems with bone resorption but also with the produc-

Dr. Carl Hansen manages the NIH Animal Genetic Resource with the help of a computer network that allows technicians to enter information directly from their work areas in the animal rooms.

Ernie Branson, NCRR

tion of the lymphokine interleukin-2, which is a mediator of many immune functions. Rats that are homozygous for the diabetes insipidus gene lack the hormone vasopressin, which is essential for maintaining a proper water balance and also appears essential for maintaining tolerance to alcohol. These mutant rats are therefore intolerant to alcohol. The rats are being used in behavioral studies as well as in research on the basis for chemical addiction. A rat model for insulin-dependent diabetes mellitus has also been developed by the staff at NIHAGR.

The NIHAGR maintains a major collection of mutant rat stocks. Work to establish these mutants onto different strains is under way. The new rat strains will be useful for developing linkage maps of genes in the rat that will benefit comparative studies with the human genome.

Electronic Management of Breeding. An electronic data processing system is currently being developed to assist in the ongoing management of the reproductive cycle of the many animal species maintained in the NIHAGR. The system's design allows performance of many functions specifically required to develop and maintain inbred strains, outbred stocks, mutant stocks, and others. It can also track four genetically determined traits concurrently in the same closed breeding group.

Touch-screen terminals are located in each animal room and are connected to a minicomputer. Technicians may input information directly from their work areas into the computer, so data sets for each animal and the data base for the colony are updated continuously and concurrently. During the first year of the system's operation the quality of colony management has improved markedly because the colony manager has online access to the current and historical information about each breeding group. This information is critical to detecting potential problems before they seriously impact on the colony. The system has also allowed colony size to be reduced in some cases.

Cryopreservation of Embryos. NIHAGR staff has developed and is maintaining an embryo bank for the various species maintained. The bank relies on cryopreservation, or freezing, to conserve embryos. The program is currently storing mouse and rabbit embryos and is starting to store rat and hamster embryos.

Embryo banking is useful for a number of reasons. Maintaining frozen embryos is considerably less costly than maintaining the animal itself. For populations of animals that are potentially useful for studying human disease but are not required immediately, freezing allows the line to be conserved. Cryopreservation also reduces the problem of genetic drift, the tendency of an animal colony to change genetic characteristics over time because changes may be introduced with each new generation. The bank may one day assure that all animals used in a particular research project are genetically identical.

Aging and Dietary Restriction

Numerous rodent studies have shown that if food intake is restricted, the rate of aging is decreased. To determine if this nutritional manipulation produces the same effect in nonhuman primates, in which data may be more relevant to humans, the VRP is working in collaboration with the National Institute on Aging to study the effects of diet restriction on aging in male rhesus and squirrel monkeys.

Two populations, juveniles and adults, of each monkey species are being used for the study. Half of the animals in each age group receive as much food as they will consume; the other half receive 30 percent less than that amount. The restriction was introduced gradually over a 3-month period.

During the first year of the study there have been findings related to aging in both populations of monkeys. These include a reduction in the concentration of lymphocytes, a reduction in the levels of several enzymes, and changes in blood chemistry. As the study continues, the researchers hope to determine if dietary restriction slows the rate of these age-related changes.

Evaluation of New Antifungal Agents

Granulocytopenia is the major predisposing factor to infection in patients treated with cytotoxic chemotherapy for neoplastic diseases. Appropriate animal models of persistent granulocytopenia are essential for development of effective antibacterial, antifungal, and immunomodulatory drugs for the prevention and treatment of infections in cancer patients. During the last decade considerable progress has been made in treating the bacterial infections that develop in granulocytopenic patients, but the treatment of invasive fungal infections has remained problematic. Amphotericin B, the cornerstone of antifungal therapy for disseminated candidiasis and other fungal infections, is frequently associated with side effects at therapeutic doses, and the selection of other drugs has been limit-

Supervisory laboratory technician Billy Barnes is working with rats in germ-free isolator.

Ernie Branson, NCRR

ed. Recently, however, fluconazole, cilofungin, and several other novel antifungal compounds and recombinant cytokines such as granulocyte colony-stimulating factor are becoming available for clinical trials or experimental evaluation.

Studies of experimental chronic granulocytopenia and prevention of its complications in laboratory animals have been limited by the lack of venous access necessary to support such immunocompromised animals. VRP scientists in cooperation with researchers at the pediatric branch of the National Cancer Institute have developed a method of chronic central venous catheterization that allows the induction, maintenance, and support of persistent granulocytopenia in rabbits. This animal model has provided a means for evaluating the efficacy of numerous antifungal agents or combinations of drugs in a variety of organ systems such as the brain, the liver, and the kidney. The effectiveness of the drugs may be monitored when they are used preventively or in early or late phases of an infection. Continuous versus intermittent infusion also may be compared, and the data extrapolated to the granulocytopenic patient. The animal model has provided a rational experimental basis for utilizing immunomodulatory therapy to shorten the duration and depth of granulocytopenia, thereby preventing invasive candidiasis and other fungal infections. In addition, the studies have built a scientific foundation for developing intramural and multicenter clinical trials for the prevention and treatment of invasive fungal infections in patients with cancer or AIDS.

Drug Infusion Into the CNS

Intrathecal injection of anticancer drugs like methotrexate and cytarabine into the cerebrospinal fluid is used in treating meningeal cancers. The standard method of administering these chemotherapeutic agents is by intermittently injecting large doses into the lumbar space. This method initially yields a very high drug concentration in the cerebrospinal fluid (CSF), but the concentration rapidly falls below the minimal cytotoxic level. In an alternate method, which would circumvent the limitations of intermittent therapy, the drugs might be introduced by continuous infusion. A continuous intrathecal infusion would avoid the initial very high CSF concentrations and maintain minimal cytotoxic concentrations in the CSF for a prolonged period.

VRP and National Cancer Institute researchers have developed a modified ventricular tube for chronic implantation into the lateral ventricle of the brain in rhesus monkeys. This tube is connected to a subcutaneous port that allows continuous infusions by pumps fitted in jackets worn by the monkeys. A second catheter, placed in the fourth ventricle and attached to a reservoir, allows for administration of large single doses and repetitive CSF sampling in unanesthetized monkeys. This technique may one day lead to the development of continuous intraventricular infusion procedures for treatment of meningeal cancers in humans and as a research tool for studies of the distribution and elimination of drugs from the CSF.

Liver Biopsy

Chronic hepatitis B is a prevalent viral disease in humans. Animal models to study the disease and assess antiviral drugs include the Pekin duck. VRP scientists have developed a technique in the experimental use of this duck that allows multiple liver biopsies and causes minimal liver damage.

The duck is anesthetized using drugs known to be safe even in the presence of liver disease. A cutaneous punch is used to obtain the biopsy. The sharp cutting edge of the punch produces minimal liver damage and hemorrhage. The ability to perform repeated biopsies makes it possible to monitor progress of the disease and the efficacy of drugs over time.

Cranial Bone Repair

The repair of large cranial bone defects is a difficult surgical problem when treating some cranial tumors, head trauma, and congenital defects. Repair is often accomplished by removing some of the patient's bone from a distant site and transplanting it to the head or by using other bone preparations or nonbone material. All of these solutions have certain problems.

VRP scientists and colleagues at NIH and Georgetown University School of Medicine in Washington, D.C., have used a monkey model with cranial malformations to show that fresh-frozen fetal bone together with bone paste from other monkeys of the same species can be used very successfully to repair the defect. Bone grafts that were performed either in utero or within 1 to 2 weeks following birth developed a strong union with the rest of the cranial bones, had a smooth surface, and provided good cosmetic results. Surgery delayed until the monkey was 2 to 3 months old resulted in rejection of the graft.

New surgical techniques are being tested in the VRP surgical unit. Surgeons from the National Heart, Lung, and Blood Institute are seen transplanting a pig heart.

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